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Emergency care drugs' chemical stability after eight weeks' deployment in the prehospital setting

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ABSTRACT

Temperature conditions vary in emergency service vehicles, which may pose a risk to the integrity of the drugs on board, possibly rendering them ineffective and increasing morbidity and mortality in patients.

Aim: This study assessed the stability of four emergency care drugs (adrenaline, etomidate, ketamine, and rocuronium) after eight weeks of deployment in the prehospital context.

Methods: The study adopted a longitudinal quantitative design to evaluate the chemical stability of emergency care drugs. The study was conducted at four emergency medical service bases in Ballito, Durban and Pietermaritzburg, South Africa. The primary outcome was the relative reduction in drug concentration from the labelled concentration after four and eight weeks. High-performance liquid chromatography-mass spectrometry (HPLC-MS) analysed samples to determine the concentration of active ingredients in the drug samples.

Results: HPLC analysis was done on 176 samples. The ambient temperature ranged from 18.7 to 44 °C in the first four weeks, averaging 26.8 °C ± 3.0. At 4 and 8 weeks, Adrenaline decreased 24.93 % and 22.73 %, respectively. Etomidate's control had 3.06 mg/ml, not the 2 mg/ml on the bottle. After 4 and 8 weeks, the samples had 3.10 and 3.15 mg/ml active components, respectively. Ketamine degraded over 30 % after four weeks but not beyond that. The Ketamine package states 10 mg/ml. However, we found 17.46 mg/ml. Rocuronium was 6.45 mg/ml in the control, although the manufacturer specified 10 mg/ml. At four weeks, the concentration was 6.70 mg/ml; at eight weeks, 6.56.

Conclusion: This study suggests that adrenaline and ketamine degrade by more than 20 % within four weeks of deployment in the prehospital field, whereas etomidate and rocuronium remain stable after eight weeks.

Introduction

Prehospital emergency care providers carry various emergency care drugs in their emergency service vehicles, whether an ambulance or a response vehicle. Their registration categories limit the number of drugs each practitioner can have. The Emergency Care Practitioner (ECP) is the highest registration category of the Health Professions Council of South Africa's Professional Board for Emergency Care, having completed a four-year undergraduate emergency care degree or a three-year diploma and a two-year part-time degree [1]. These ECPs transport a range of drugs, kept in drug bags in the trunk or backseat of the response vehicle or the ambulance. Some pharmaceuticals, such as lorazepam and succinylcholine, must be kept refrigerated (2–8 °C), yet refrigerators may not be available in some emergency vehicles that transport these drugs [2]. Other drugs, such as benzodiazepines, must be stored at room temperature (25 °C). However, the temperature in the prehospital setting is unpredictable and can reach well over 30 °C during the summer months [3]. As a result, storing drugs in emergency service vehicles leaves them prone to degradation owing to prolonged exposure to high temperatures [4].

Sunlight and extreme temperatures are essential stressors for drugs that can result in losing biological potency, with temperature being the most crucial factor [5]. The mean kinetic temperature (MKT) is a weighted average temperature that quantifies the comprehensive impact of temperature fluctuations on drug substances. Because it considers the effect of temperature on the velocity of a chemical reaction, the MKT is, by definition, more significant than the arithmetic average temperature. Extreme temperatures degrade pharmaceuticals through chemical reactions such as dehydration, hydrolysis, and oxidation, thereby diminishing drug efficacy [5]. Drugs are subjected to stability

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tests at various temperatures so that the manufacturer can guarantee their efficacy when appropriately stored, typically at ambient temperature or in the refrigerator. Temperature variations in emergency service vehicles pose a risk to the integrity of the drugs on board, which could render them ineffective and increase patient morbidity and mortality [6]. However, it would be difficult to ascertain whether a patient does not react to a drug due to the severity of the underlying condition or due to a lack of drug potency caused by temperature-induced degradation.

The outcomes of studies on the effects of environmental exposure on emergency care drugs have provided mixed results [2,4–8]. When refrigerated drugs such as lorazepam and succinylcholine were deployed in the prehospital situation, degradation was observed, while certain pharmaceuticals showed little to no degradation [4,7,8]. Stein's study in Johannesburg observed that the MKT exceeded the controlled room temperature for six months [9]. However, the study did not assess chemical degradation [9]. To our knowledge, no study has investigated the chemical degradation of emergency care drugs in the African prehospital setting. This study assessed the chemical stability of four emergency care drugs (adrenaline, etomidate, ketamine, and rocuronium) after eight weeks of deployment in the prehospital setting.

Methods

Study design and setting

The study utilised a quantitative design to evaluate the chemical stability of emergency care drugs (see Table 1) under actual prehospital conditions. All of these drugs are available to ECPs in South Africa.

The research was conducted at four emergency medical service bases in South Africa: Ballito, Durban (two bases), and Pietermaritzburg. The respective emergency medical service providers operate a 24-hour, seven-days-a-week service. Because the ambient room temperature fluctuates and may exceed the manufacturer's storage recommendation of 25 °C, it was determined that the controls would be stored in the refrigerator (4 to 8 °C) until analysis. The drugs used as samples in the study were kept in drug bags in the vehicle used by the ECP, whether an ambulance or a response vehicle. The drugs were not expired and were maintained in secured drug bags that only the researchers could access. The various emergency medical services (EMS) provided gatekeeper approval. Arrangements were made with the respective base managers to meet with the ECPs to discuss the study. At this point, the drug bags were left with each ECP, who were shown what was inside the drug bags before they were locked.

After four and eight weeks of deployment, three samples of each drug were removed from the drug bags and placed in the refrigerator pending analysis.

Sample size

Eleven ECPs from Ballito, Durban, and Pietermaritzburg were included in the study. Logistics constrained the design of this *in-vivo* trial. Firstly, the paramedic units selected had to be in an area with known relatively high ambient temperatures. Secondly, the units had to be known to the investigator to be cooperative and reachable. Therefore, units in the Durban and Pietermaritzburg areas were chosen. The last consideration was funding, with the cost of the material and laboratory analyses to be considered. This was why the trial was limited to 11 paramedic units.

Table 1
Pharmaceutical drug list.

Drug name	Expiration	Total concentration (mg/ml)	Recommended Storage (°C)	Batch Number
Adrenaline	August 2022	1 mg/ml	At or Below 25	121,269
Etomidate	April 2022	2 mg/ml	At or Below 25	T026642
Ketamine	April 2025	10 mg/ml	At or Below 25	90PE064
Rocuronium	May 2023	10 mg/ml	2–8	Y44Y

Procedures

A Temp U03 temperature humidity logger was used to measure the temperature in each drug bag every ten minutes. The Temp U03, temperature humidity logger, also provided the MKT at the end of the study period. The concentration of active components in drug samples was determined using high-performance liquid chromatography-mass spectrometry (HPLC-MS).

At the end of the 8-week research period - 01 February to 31 March 2021 - the drugs were judged stable at concentrations exceeding 90 %. DLD Scientific (Durban, South Africa) provided the reference standards and LC-MS grade solvents (acetonitrile and water). A series of calibration standards in 40 % acetonitrile were prepared using reference standards for each drug. Drug samples (0.5 mL aliquots) were chilled in 1 mL amber vials during storage. Samples were cooled to room temperature before being analysed using an isocratic elution technique with 40 % acetonitrile. For all drug samples, an injection volume of 5 μL was employed. For each drug, control samples were run under similar operational conditions. All samples were tested in duplicate, and the average concentration for each site was reported.

Data analysis

Microsoft Excel (Microsoft Corp., Redmond, WA) was used to manage the data. Means and standard deviations were used to measure data central tendency and dispersion for normally distributed variables and medians and interquartile ranges for skewed variables. The null hypothesis that drug concentrations do not change over eight weeks while controlling for temperature exposures was tested using repeated measurements of analysis of covariance. The significance threshold was set at 0.05.

Results

A total of 176 samples were collected, and HPLC analysis was performed. During the study period, the average MKT was 26.4 °C ± 1.4. During the first four weeks, the ambient temperature ranged from 18.7 to 44 °C, with a mean of 26.8 °C ± 3.0. During the eight weeks, the temperature ranged from 16.5 to 46.7 °C, with a mean of 26.3 °C ± 3.2. Table 2 shows the concentrations of the four drugs after four and eight weeks. The concentration of Adrenaline on the vial label was 1 mg/mL, which was also noted when the control was performed. However, after four weeks, the samples' Adrenaline concentration dropped to 0.75 mg/ml and 0.77 mg/ml after eight weeks. This represented a decrease of 24.93 % and 22.73 % at 4 and 8 weeks, respectively. For Etomidate, we discovered that the control had a concentration of 3.06 mg/ml rather than the 2 mg/ml reported on the bottle. The active ingredient concentration in the samples was 3.10 mg/ml after four weeks and 3.15 mg/ml after eight weeks. After four weeks, Ketamine showed greater than 30 % degradation, but none after that. Although the packaging for Ketamine indicates a concentration of 10 mg/ml, we discovered 17.46 mg/ml. The control for Rocuronium was 6.45 mg/ml, while the specified concentration was 10 mg/ml. At four weeks, the concentration was 6.70 mg/ml; at eight weeks, it was 6.56 mg/ml.

A one-way analysis of covariance revealed that temperature had no effect on drug concentration over the study period ($p = 0.24$). No significant drug degradation occurred between four and eight weeks ($p = 0.60$).

Discussion

To our knowledge, this is the first study to investigate the stability of

Table 2
Drug concentrations after four- and eight-week deployment.

Drug	Site	Sample Concentration (mg/ml)		% Degradation		Control Concentration (mg/ml)	Mean Temperature °C	
		4 weeks	8 weeks	4 weeks	8 weeks		4 weeks	8 weeks
Adrenaline	1	0.76 ± 0.03	0.81 ± 0.00	24.01	18.73	1.00	27.2 ± 3	26.7 ± 2.7
	2	0.67 ± 0.02	0.73 ± 0.00	32.87	27.13	1.00	24.2 ± 1.6	24.3 ± 3.6
	3	0.77 ± 0.10	0.84 ± 0.06	23.27	16.46	1.00	28 ± 3.8	27 ± 3.9
	4	0.80 ± 0.00	0.71 ± 0.01	19.58	28.54	1.00	25.9 ± 2.7	25.4 ± 2.6
Mean		0.75 ± 0.05	0.77 ± 0.05	24.93	22.71		26.8 ± 3.0	26.3 ± 3.2
Etomidate	1	2.98 ± 0.03	3.15 ± 0.09	2.37	−3.15	3.06	27.2 ± 3	26.7 ± 2.7
	2	3.02 ± 0.13	3.10 ± 0.01	1.33	−1.57	3.06	24.2 ± 1.6	24.3 ± 3.6
	3	3.00 ± 0.05	3.15 ± 0.05	1.94	−3.02	3.06	28 ± 3.8	27 ± 3.9
	4	3.41 ± 0.01	3.19 ± 0.08	−11.70	−4.42	3.06	25.9 ± 2.7	25.4 ± 2.6
Mean		3.10 ± 0.18	3.15 ± 0.03	−1.40	−2.93		26.8 ± 3.0	26.3 ± 3.2
Ketamine	1	12.13 ± 0.00	12.83 ± 0.12	30.50	26.48	17.46	27.2 ± 3	26.7 ± 2.7
	2	11.84 ± 0.01	13.41 ± 0.40	32.19	23.18	17.46	24.2 ± 1.6	24.3 ± 3.6
	3	12.21 ± 0.56	13.27 ± 0.00	30.07	23.98	17.46	28 ± 3.8	27 ± 3.9
	4	11.84 ± 0.11	12.40 ± 0.13	32.19	28.96	17.46	25.9 ± 2.7	25.4 ± 2.6
Mean		12.00 ± 0.17	13.27 ± 0.00	31.25	26.22		26.8 ± 3.0	26.3 ± 3.2
Rocuronium	1	6.46 ± 0.06	6.55 ± 0.16	0.08	−1.47	6.45	27.2 ± 3	26.7 ± 2.7
	2	6.76 ± 0.13	6.62 ± 0.10	4.81	−2.56	6.45	24.2 ± 1.6	24.3 ± 3.6
	3	6.98 ± 0.04	6.50 ± 0.11	8.14	−0.70	6.45	28 ± 3.8	27 ± 3.9
	4	6.60 ± 0.02	6.60 ± 0.02	2.25	−2.25	6.45	25.9 ± 2.7	25.4 ± 2.6
Mean		6.70 ± 0.19	6.56 ± 0.05	−3.82	−1.74		26.8 ± 3.0	26.3 ± 3.2

Mean ±Standard Deviation.
A negative degradation means that the sample concentration is higher than the control.

EMS drugs after deployment in a pre-hospital setting in Africa. While there is evidence that some pharmaceuticals are unaffected by the uncontrolled prehospital environment, none of the research was conducted in the African setting, which has a different climate than the global north [2,5,8,10]. Previous research has demonstrated that heat and cold impact drugs [4,6,11]. In our research, we discovered a commonality. The high temperatures in the study area potentially affected the Adrenaline and Ketamine samples, resulting in a drop in the active ingredient content.

Our findings differ from those of De Winter et al., who discovered that adrenaline remained stable for at least a year while stored at room temperature and in the emergency physician transport vehicle [2]. One possible explanation for this disparity is that our study had greater temperatures, with a maximum of 46.7 °C compared to 35.3 °C, with a mean of 26.3 °C and 10.3 °C. Furthermore, the vehicles in their research were kept in a partially temperature-controlled garage [2]. This was not the case in our investigation, as vehicles were kept outside. The call volume may also influence the car's position, as fewer calls imply the vehicle sits stationary for extended periods in the heat. While some ambulances may have air conditioning, they may not always be operational. Another study found that after eight weeks of exposure to either cold (5 °C) or hot (70 °C) temperatures for eight-hour periods each day, adrenaline (1:10 000) experienced considerable degradation and loss of the parent component [12]. Adrenaline degraded by 64 % in their 12-week trial [12]. In their study, Church et al. discovered that the degradation of adrenaline depends on the sodium metabisulfite content and the temperature exposure duration in their investigation [13].

For Etomidate and Ketamine, we noticed a rise in the concentration of the active ingredient in the control. One probable explanation is that because the investigation was performed with HPLC-MS, it is possible that a derivative with the same mass as the active component was discovered, resulting in a larger concentration.

Foertsch et al. investigated the degradation of ketamine during six months of exposure to moderate and high-temperature settings in a recent study [10]. During the study period, they discovered no significant change in concentration. However, their study utilised 50 mg/ml of ketamine, whereas ours used 10 mg/ml, which could explain the discrepancy in results.

Surprisingly, rocuronium, which must be maintained in a refrigerator between 2 and 8 °Celsius, remained stable during the study period. Nonetheless, the manufacturer recommends that rocuronium be utilised within 60 days of being removed from the refrigerator and brought to room temperature. Our research supports the manufacturer's claim that rocuronium is stable outside the fridge for 60 days. Indeed, Vermeulen et al. discovered that rocuronium deteriorated significantly only 12 weeks after being taken from the refrigerator [14].

We discovered no statistically significant effect of mean ambient temperature on drug concentration. However, this should not be mistaken with clinical significance because less than 90 % degradation is clinically significant, as with adrenaline and ketamine. This could explain why the pharmacology literature recommends using MKT rather than mean ambient temperature to measure the drug stability [4]. Furthermore, De Winter et al. discovered identical deterioration rates in winter and summer. They claimed that the most significant factor causing degradation is environmental temperature exposure incompatible with the manufacturer's suggestion [2].

At four and eight weeks, the etomidate and rocuronium sample concentrations were higher than the control concentrations. The investigation also discovered that the etomidate control concentration was greater than the manufacturer's indicated amounts, while the ketamine concentration was roughly 7 mg higher. It is disturbing that we discovered drug concentrations that differed from those listed on the label, with ketamine being the most anomalous at 7 mg greater. This may result in patients being overdosed inadvertently. Rocuronium was approximately 4 mg lower than the label concentration, which may result in the under-dosing of the patient.

Our findings imply that EMS drug storage and restocking strategies should incorporate drug storage methods that minimise the impact of environmental exposure while adhering to the manufacturer's suggested storage recommendations. Otherwise, it may be prudent to retain drugs such as adrenaline and ketamine in the field for no more than four weeks, as degraded drugs have been reported to lose clinical efficacy, compromising patient treatment [15].

There are various limitations to this study. Although our findings may apply to places with similar climates to the one employed in this study, the prehospital environment is uncontrolled. Drug storage at room temperature or under refrigeration can only be guaranteed once specific storage protocols are established. While temperature is the most critical factor in drug degradation, other factors, such as sunshine, can also induce degradation. Nonetheless, these were outside the focus of our research. The biological activity of the drugs was not studied as part of this investigation; therefore, we cannot determine their potency or

direct clinical impact. Cairns et al., on the other hand, discovered that the chemical degradation of adrenaline is followed by reduced human physiologic responses to the substance [15]. A final limitation was that the controls were not measured upon delivery because they were presumed adequate. After all, they were stored according to the manufacturer's instructions. Instead, they were measured at eight weeks with the remainder of the sample drugs.

Conclusion

This study found that adrenaline and ketamine deteriorate by more than 20 % within four weeks of deployment in the prehospital field, whereas etomidate and rocuronium remain stable after eight weeks. However, the control concentrations for etomidate, ketamine, and rocuronium differed from the manufacturer's indicated amounts. Another study is needed to assess the long-term stability of other drugs utilised in the prehospital context.

Dissemination of results

The results were disseminated to the respective EMS organisations participating in the study.

Author contributions

Author contributions to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; the crafting of the work or critical revision for important intellectual content include the following: 60% of the contribution was made by SS, 20% by TS, and 20% by KK. All authors authorised the final manuscript version.

Declaration of Competing Interest

The author declared no conflicts of interest.

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