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Brief Report

Stability of Drugs Used in Helicopter Air Medical Emergency Services: An Exploratory Study

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A B S T R A C T

Objective: Transportation by air exposes drugs used in emergency medical services to vibrations. The aim of the study was to determine whether or not vibrations caused by a helicopter induce the degradation of 5 drugs used in this setting.

Methods: A longitudinal study in an operating medical helicopter along with a worst case was conducted. The studied drugs were 3 drugs labeled for refrigeration (cisatracurium, lorazepam, and succinylcholine) and 2 albumin solutions (human albumin 4% and 20%). These drugs were stored for 4 months according to the following conditions: inside a helicopter, worst case with exposure to extreme vibrations, at room temperature, and according to manufacturers' recommendations. Samples were analyzed with validated high-performance liquid chromatography assay methods. A drug was considered stable if the remaining drug content was above 90% of the label claim. Except for the albumin solutions, visual inspection was used to determine instability by the formation of aggregates.

Results: Only the samples stored at room temperature became unstable after 4 months. No difference in extreme foaming was observed in the albumin solutions.

Conclusions: These data suggest that the effect of degradation of drugs caused by vibrations is negligible. Temperature was observed as the main cause of drug degradation.

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The impact of temperature exposure on drug deterioration during ground transportation for the delivery of emergency medical services (EMS) has already been studied in real-world settings.^{1–3} However, no studies were performed thus far to determine the impact of vibrations on drug stability in ground or in air medical transportation. Although the underlying mechanism remains unclear, vibrations may affect drug stability as a result of the initial rise in temperature caused by energy expenditure or as a result of interactions with surfaces (eg, vial-water interfaces).^{4–6} Previous studies showed that cisatracurium, lorazepam, and succinylcholine,

when exposed to prehospital conditions, became unstable in a few weeks or months, suggesting that these might also be susceptible to vibrations.^{2,3} Cisatracurium and succinylcholine are both muscle relaxants and are used to assist endotracheal intubation. Lorazepam is used to treat status epilepticus. Furthermore, it is described that most proteins, including albumin solutions, form precipitates by adsorption to solid surfaces when sufficient agitation or shear forces are introduced.⁵ Albumin 4% and 20%, both albumin solutions, are used as fluid resuscitation in patients with sepsis. Vibration is inherent to all transport vehicles, but it has been shown that air transfers are characterized by higher frequencies and higher lateral (side to side) and anterior-posterior (chest to back) accelerations; however, these are considered as more stable vibrations compared with ground transportation.⁷

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Table 1
List of Drugs Studied

Drug Name	Brand Name (Manufacturer)	Concentration Volume	Expiration Date	Batch Number	Storage Recommendation According to Manufacturer
Cisatracurium besylate	Nimbex (GlaxoSmithKline, Wavre, Belgium)	2 mg/mL-10 mL	05-2015 07-2015 ^a	3509 3514 ^a	Refrigeration
Lorazepam	Temesta (Pfizer, Brussels, Belgium)	4 mg/mL-1 mL	02-2014 05-2016 ^a	4011 4511 ^a	Refrigeration
Succinylcholine chloride	Celocurine (CSP Benelux, Houdeng-Goegnies, Belgium)	50 mg/mL-2 mL	05-2014 08-2015 ^a	1470192 1551284 ^a	Refrigeration
Human albumin	SOPP-SSPP (C.A.F.-D.C.F., Brussels, Belgium)	4%: 400 mL	06-2015 08-2016 ^a	13F07C 14H13C ^a	Room temperature
Human albumin	Albumine (C.A.F.-D.C.F., Brussels, Belgium)	20%: 100 mL	12-2014 04-2016 ^a	12L10C 14D23C ^a	Room temperature

^a Used in the worst-case scenario performed on December 10, 2014, for the drugs labeled for refrigeration and on December 11, 2014, for the albumin solutions.

The aim of this study is to determine whether vibrations caused by helicopter transport results in the degradation of these 5 essential drugs used in helicopter emergency medical services (HEMS).

Materials and Methods

Study Design

A longitudinal study along with a worst-case scenario simulation was performed to evaluate the stability of drugs that are used in HEMS. The studied drugs were 3 drugs labeled for refrigeration, including cisatracurium, lorazepam, and succinylcholine, and 2 albumin solutions (albumin 4% and 20%). These drugs, except for albumin 20%, are used in our emergency drug kit.

Study Setting and Environment

This longitudinal study was conducted at the emergency department where a platform was operational since 2013 to perform HEMS for urgent transports between different hospitals by helicopter. This helicopter (EC135T1, Airbus) has 2 turbines, a speed of 240 km/h, and a main rotor with 4 blades rotating at 412 rpm. The worst-case scenario simulation was conducted by the department of mechanical engineering.

Experimental Protocol

During a 4-month period, the drugs labeled for refrigeration (cisatracurium, lorazepam, and succinylcholine) were stored in 3 places: in a refrigerator, at room temperature, and in the helicopter. Albumin 4% and albumin 20% were stored at 2 places: at room temperature and in the helicopter. Details of the studied drugs can be found in Table 1. Refrigerator ampoules were stored in a refrigerator located in the hospital pharmacy equipped with an automatic temperature monitoring system. Room temperature and helicopter ampoules were placed into the regular drug box in the portable EMS backpack and stored, respectively, either in the emergency department or on the floor of the helicopter under the seat of the pilot where they were protected from ultraviolet exposure caused by direct sunlight. These ampoules were not used for treatment in patients; the backpacks were locked and labeled “not for human use.” Thermometers with memory were placed within the backpacks (Escort Intelligent MiniPlus, Leiria, Portugal) to log the temperatures. At regular time intervals, the loggers were changed to avoid empty batteries and a full memory. All recordings were sampled at least once per 60 minutes to cover temperature registration during the flights.

The worst-case scenario was set up to simulate long-term continuous exposure to vibrations and was conducted using an electromechanical shaker. The setup is based on the experience of the staff of the department of mechanical engineering. The

6-dimensional vibration in the helicopter was approximated by a 1-dimensional vibration with a frequency of 27 Hz and a root mean square acceleration amplitude of 1.5 m/s² during a period of 8 hours. The frequency and amplitude are based on exposure levels reported in the literature, and the exposure duration is based on the International Organization for Standardization, ISO 2631-1 for employees.⁷⁻⁹ For cisatracurium, lorazepam, and succinylcholine, a cooling element was added to the backpack to solely evaluate the impact of vibrations and eliminate the effect of temperature.

We used 3 samples of each drug labeled for refrigeration and 1 sample of each albumin solution, respectively, for each condition. The reason for the different approach for albumin solutions was the larger volume of samples of these drugs.

Measurements

At the end of the study period and for the 4 storage conditions (refrigerator, room temperature, helicopter, and worst case), the concentration of cisatracurium, lorazepam, and succinylcholine was determined by high-performance liquid chromatography. Detailed experimental conditions of the assay are described elsewhere.³ The drug content was reported as a percentage of the label claim, with the relative standard deviation of the measurements. For the albumin solutions, visual inspection of precipitate formation was performed.

Key Outcome Measures

The key outcome measurement was the stability of the included drugs stored in a helicopter and exposed to extreme vibrations. Cisatracurium, lorazepam, and succinylcholine were considered to be stable at contents above 90% of the label claim. The refrigerated samples served as control samples, and the samples stored at room temperature were used in order to take into account the factor “temperature.” Albumin solutions were considered to be stable when no aggregate formation was found by visual inspection. For the albumin solutions, the samples stored at room temperature served as controls.

Data Analysis

SPSS version 23.0 (SPSS, Chicago, IL) for Windows software (Microsoft, Redmond, WA) was used for statistical analysis. *P* values were calculated using the unpaired *t*-test or 1-way analysis of variance to compare the mean content of 2 or more conditions for each individual drug. Pair-wise comparisons were performed for statistically significant differences from analysis of variance with the Tukey post hoc test. *P* values of .05 or less were deemed to be statistically significant.

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