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BRIEF REPORT

The Impact of Freeze-Thaw Cycles on Epinephrine

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Objectives.—Epinephrine is the first-line medical treatment for anaphylaxis, a life-threatening allergic syndrome. To treat anaphylaxis, backcountry recreationalists and guides commonly carry epinephrine autoinjectors. Epinephrine may be exposed to cold temperatures and freezing during expeditions. An epinephrine solution must contain 90% to 115% of the labeled epinephrine amount to meet United States Pharmacopeia standards. The purpose of this study was to determine whether freeze-thaw cycles alter epinephrine concentrations in autoinjectors labeled to contain 1.0 mg/mL epinephrine. A further objective was to determine whether samples continued to meet United States Pharmacopeia concentration standards after freeze-thaw cycles.

Methods.—Epinephrine from 6 autoinjectors was extracted and divided into experimental and control samples. The experimental samples underwent 7 consecutive 12-hour freeze cycles followed by 7 12-hour thaw cycles. The control samples remained at an average temperature of 23.1°C for the duration of the study. After the seventh thaw cycle, epinephrine concentrations were measured using a high-performance liquid chromatography assay with mass spectrometry detection.

Results.—The mean epinephrine concentration of the freeze-thaw samples demonstrated a statistically significant increase compared with the control samples: 1.07 mg/mL (SD ± 8.78; 95% CI, 1.04 to 1.11) versus 0.96 mg/mL (SD ± 6.81; 95% CI, 0.94 to 0.99), respectively. The maximal mean epinephrine concentration in the experimental freeze-thaw group was 1.12 mg/mL, which still fell within the range of United States Pharmacopeia standards for injectables (0.90 to 1.15 mg/mL).

Conclusions.—Although every attempt should be made to prevent freezing of autoinjectors, this preliminary study demonstrates that epinephrine concentrations remain within 90% to 115% of 1.0 mg/mL after multiple freeze-thaw cycles.

Key words: anaphylaxis, epinephrine, adrenaline, autoinjector, drug stability

Introduction

Anaphylaxis is a life-threatening allergic syndrome that may be triggered by an insect sting, contact with certain plants or other substances, medications, and certain foods. It is estimated that 1% to 2% of the general population is at risk for anaphylaxis, and that the global prevalence of those with epinephrine prescriptions may be as high as 2%.[1] Epinephrine is the first-line medical treatment for anaphylaxis, and administering epinephrine can rapidly reverse bronchospasm and other life-threatening manifestations of the reaction.

Backcountry recreationalists and guides commonly carry epinephrine in the form of an epinephrine autoinjector. The adult dose autoinjector is a single-use, self-administered mechanical device that delivers 0.3 mL of 1:1000 concentration epinephrine (0.3 mg) intramuscularly via a spring-loaded needle and syringe. In the United States and Canada, one such autoinjector (Figure 1) is marketed under the trade name EpiPen.[2] Those who are known to be severely allergic to specific triggers or have experienced anaphylaxis in the past should carry autoinjectors, or another form of epinephrine, with them in the wilderness. In addition, wilderness guides and instructors should consider carrying epinephrine in their medical kits to address unexpected anaphylactic reactions in the backcountry.[3]

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Figure 1. EpiPen autoinjector that has been disassembled to show internal ampule. Solution has been removed.

In backcountry environments, epinephrine formulations may be exposed to extreme temperatures. The manufacturer of EpiPen provides prescribing information for the labeled recommended storage, which is protection from ultraviolet light and storage between 20°C and 25°C with excursions permitted to between 15°C and 30°C.[2] The manufacturer recommends replacing the product if it has been accidentally refrigerated. This may not be possible on an extended backcountry expedition.

It is well established that epinephrine solutions are unstable when exposed to high temperatures (ie, in excess of 25°C) or exposure to direct ultraviolet light.[4] Epinephrine also has a limited shelf life, with significant degradation occurring after expiration of drug samples.[5] However, it has been reported in previous literature that epinephrine solutions within expiration dates are stable in refrigeration and at cooler temperatures, and refrigeration even has been described as a technique to prolong shelf life of epinephrine solutions,[4] despite current manufacturer recommendations. For example, when epinephrine was cooled to 2.5°C and subsequently returned to room temperature (23°C), there was no statistically significant change in concentration of epinephrine.[6] In another study, Zenoni et al[7] stored epinephrine solutions in Luer-lock syringes at temperatures between 2°C and 8°C for up to 24 weeks and detected no degradation of epinephrine. In the current literature, there are no studies addressing epinephrine stability after a single freeze or after multiple freeze-thaw cycles.

The purpose of this study is to determine whether there is a change in epinephrine concentration after samples are exposed to freezing temperatures followed by thawing. These results will help guide the use of epinephrine autoinjectors while on backcountry expeditions in cold environments where freezing may be unavoidable. Based on previous literature and knowledge that epinephrine degradation reactions of oxidation and sulfonation happen more readily when the compound is exposed to heat and light, we hypothesized that epinephrine concentration would not be affected by freezing temperatures (Figure 2).

Methods

PREPARATION AND STORAGE OF EPINEPHRINE EXPERIMENTAL AND CONTROL SAMPLES

High-performance liquid chromatography (HPLC) has been used in previous studies of epinephrine stability to determine concentration values in drug solutions.[4,5] Our

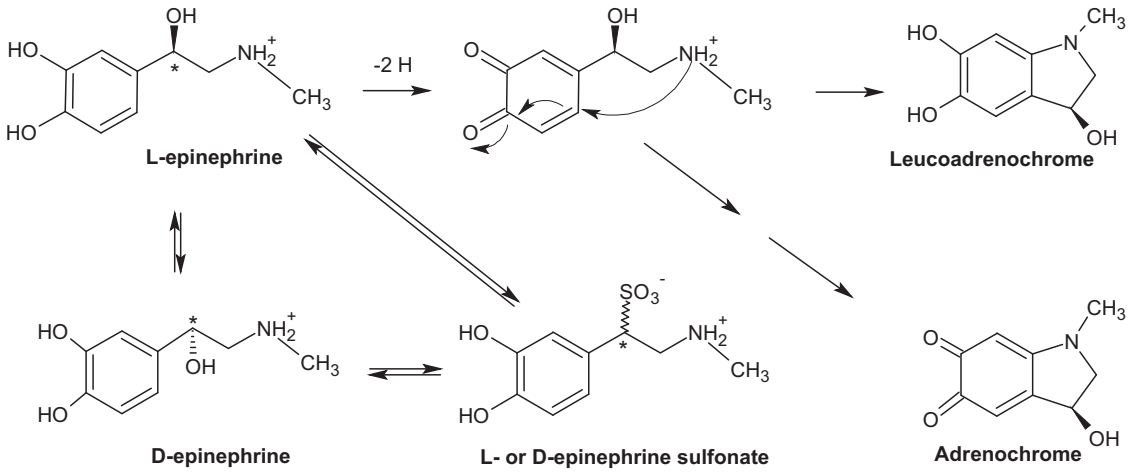

Figure 2. Degradation reactions of L-epinephrine. Adrenochrome creates a colored precipitate within epinephrine solutions. Discoloration of EpiPens indicates degradation has occurred and the autoinjector should be discarded.