Long-term stability of epinephrine dispensed in unsealed syringes for the first-aid treatment of anaphylaxis

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Background: When epinephrine autoinjectors are unavailable or unaffordable, patients at risk for anaphylaxis in the community are sometimes provided with an unsealed syringe containing a premeasured epinephrine dose for use in first-aid treatment of anaphylaxis episodes.

Objectives: To study the stability of epinephrine solution in unsealed syringes under conditions of high ambient temperature, low vs high humidity, and light vs dark.

Methods: Forty unsealed syringes each containing an epinephrine dose of 0.3 mg (as a 1-mg/mL epinephrine solution) were stored at 38°C for 5 months, with 10 syringes at each of 4 different standardized storage conditions: dark and light at low (15%) humidity and dark and light at high (95%) humidity. Duplicate syringes were removed monthly from each storage environment and analyzed for epinephrine content vs control syringes.

Results: The epinephrine dose, expressed as the percentage remaining of the mean control dose, was below compendial limits (90% to 115% of label claim) by 3 months after storage at 38°C and low humidity and by 4 months after storage at 38°C and high humidity. Light had no significant effect.

Conclusion: In hot climates, if an unsealed syringe prefilled with an epinephrine dose is provided for the first-aid treatment of anaphylaxis, it should be replaced every few months on a regular basis with a new syringe containing a fresh dose of epinephrine.

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INTRODUCTION

Epinephrine is the initial medication of choice for anaphylaxis.[1–4] The optimal dose of epinephrine for the first-aid emergency treatment of anaphylaxis has not yet been confirmed in randomized controlled trials; however, 0.3 mg given by intramuscular injection is often recommended for adults, based on clinical experience and consensus.[1–4]

In many countries, epinephrine autoinjectors for first-aid treatment of anaphylaxis episodes in the community are either unavailable or unaffordable.[5,6] In this situation, physicians have a limited number of options, which include providing patients at risk with an ampule of epinephrine and a disposable plastic 1-mL syringe,[7] or providing an unsealed, 1-mL syringe prefilled with the epinephrine dose.

Providing the epinephrine dose in a prefilled unsealed syringe raises several concerns, including the issue of stability of epinephrine solution that is exposed to conditions that might not be optimal with regard to air, temperature, humidity, and light. The aim of this study was to evaluate the effects of high ambient temperature, high or low humidity, and light or dark on the stability of epinephrine solutions drawn up from ampules into unsealed, disposable plastic 1-mL syringes and stored under these suboptimal conditions.

METHODS

Materials

Ampules from the same batch containing 1 mg/mL of epinephrine solution, with 0.9 mg/mL of sodium metabisulfite as an antioxidant (Abbott Laboratories Limited, Saint-Laurent, Quebec, Canada), were purchased from a community pharmacy. Disposable plastic 1-mL syringes and 23-gauge, 2.5-cm needles were purchased from Becton-Dickinson (Franklin Lakes, New Jersey). Silica gel, for use as a desiccant, was purchased from Anachemia Science (Montreal, Quebec, Canada).

Preparation and Storage of Prefilled Unsealed Epinephrine Syringes

We evaluated the effect of different storage conditions at high temperature (high or low humidity; light or dark) on the stability of a 0.3-mg epinephrine dose contained in prefilled syringes loaded with 0.3 mL of epinephrine solution over time (from month 0 [controls] to 5 months).

Forty-eight syringes were loaded with 0.3 mL of a 1-mg/mL epinephrine solution (1:1,000). To reduce variabil-

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ity, all the epinephrine doses, including those in the 8 control syringes and those in the 40 syringes stored under different environmental conditions, were drawn up by the same person on the same day. Air bubbles were removed to reduce epinephrine exposure to oxygen during storage. Needles were left attached and recapped. The contents of the control prefilled epinephrine syringes were ejected and immediately stored at −20°C.

Forty prefilled epinephrine syringes were randomly allocated to 1 of 4 standardized storage environments (dark and light at low [15%] humidity and dark and light at high [95%] humidity) and stored in 2 different incubators at a constant temperature of 38°C, selected to reflect a typical ambient temperature in a hot climate. One incubator was illuminated by a 40-W light bulb (light), selected to provide a source of light without increasing the temperature in the incubator, and the other had no light source at all (dark). Within each incubator, prefilled epinephrine syringes were stored in 2 sealed transparent glass containers, one containing silica gel to provide low (15%) humidity and the other containing a water bath to provide high (95%) humidity, as monitored using a psychrometer (Barigo, Villingen-Schwenningen, Germany). On a monthly basis, from month 0 (controls) to month 5, 2 prefilled epinephrine syringes were randomly selected and removed from each of the 4 different storage environments.

The volumes of solution ejected from the selected prefilled epinephrine syringes were weighed using a Mettler-AE160 analytical balance (Mettler Instrumente, Zurich, Switzerland) and stored at −20°C until analyzed. The epinephrine concentrations in the ejected volumes were measured using reverse-phase high-performance liquid chromatography with UV detection (Waters Corp, Milford, Massachusetts), the official US Pharmacopeia method for measurement of epinephrine in aqueous solutions.[8,9]

Calculation of the Ejected Epinephrine Dose and Dose Percentage Remaining in the Prefilled Unsealed Epinephrine Syringes

The epinephrine dose ejected from each prefilled epinephrine syringe was calculated by multiplying the epinephrine concentration by the ejected volume. The ejected solutions were weighed and the volume calculated gravimetrically. The mean density of a 1-mg/mL epinephrine solution (as the hydrochloride) was determined by replicate weighing of 0.1-mL volumes (Eppendorf pipette; Brinkmann Instruments Ltd, Mississauga, Ontario, Canada) and calculating the mean weight per volume. The percentage of the epinephrine dose ejected from the prefilled epinephrine syringe in each storage environment was calculated as the ratio of the mean epinephrine dose at time *t* and the mean epinephrine dose at month 0 (controls).

Statistical Analysis

The epinephrine doses ejected from the prefilled unsealed epinephrine syringes were evaluated by factorial analysis of variance, using statistical analysis software Systat 12 (Systat Software Inc, San Jose, California). Differences were considered to be statistically significant at $P < .05$. The epinephrine doses ejected, expressed as a percentage, were compared with the US Pharmacopeia compendial limits for epinephrine injections, which are 90% to 115% of label claim.[8]

RESULTS

The filling and ejection variability, calculated using the prefilled epinephrine syringes, was ±0.5%. Evaluation of the full 3-way (time, humidity, and light) factorial model demonstrated significant time ($F_{5,24} = 55.7$, $P > .05$) and humidity ($F_{1,24} = 96.2$, $P > .05$) effects but no significant light effect ($F_{1,24} = 1.9$, $P > .05$). Therefore, the model was reduced to a 2-way (time, humidity) design that demonstrated significant time ($F_{5,36} = 44.8$, $P < .05$) and humidity ($F_{1,36} = 77.3$, $P < .05$) effects and a significant time × humidity interaction ($F_{5,36} = 13.8$, $P < .05$).

Throughout the 5 months of storage at 38°C, the prefilled epinephrine syringe dose decreased under both high- and low-humidity conditions; however, the decrease was greater under conditions of low humidity (hence, the significant interaction), with differences between low and high conditions achieving statistical significance at months 3, 4, and 5 (Fig 1, Table 1).

Under high-humidity storage conditions, by the end of month 4, the prefilled epinephrine syringe dose had decreased significantly to 83% of the dose at month 0 (controls) (Fig 1, Table 1). Under low-humidity storage conditions, by the end of month 3, the prefilled epinephrine syringe dose had decreased significantly to 60% of the dose at month 0 (controls).

DISCUSSION

Epinephrine in solution is inherently unstable. Degradation occurs gradually over time, even in the presence of an anti-

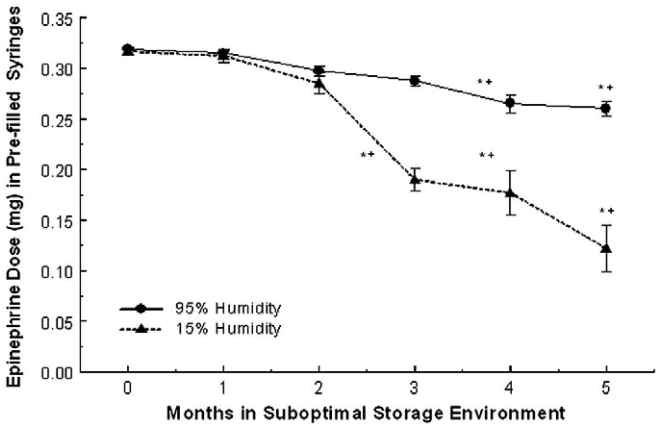

Figure 1. Mean (SEM) epinephrine dose remaining in the prefilled unsealed syringes stored at 38°C and at high or low humidity for 5 months. * $P < .05$ compared with control syringes containing 0.32 (0.00) mg. + Below the US Pharmacopeia compendial limits for epinephrine injections (90% to 115% of label claim).

Table 1. Epinephrine Doses Remaining

Time, mo	Low (15%) humidity		High (85%) humidity	
	Mean (SEM) dose, mg	% of control dose	Mean (SEM) dose, mg	% of control dose
0[a]	0.317 (0.004)	100	0.319 (0.001)	100
1	0.313 (0.006)	99	0.315 (0.003)	99
2	0.285 (0.010)	90	0.298 (0.005)	93
3	0.190 (0.011)[b]	60[c]	0.288 (0.005)	90
4	0.178 (0.023)[b]	55[c]	0.265 (0.009)[b]	83[c]
5	0.123 (0.023)[b]	39[c]	0.260 (0.007)[b]	82[c]

[a] Month 0 = control doses.
[b] $P < .05$ vs control syringes.
[c] Below the US Pharmacopeia compendial limits for epinephrine injections (90%–115% of label claim).

oxidant, such as sodium metabisulfite, and even if the solution is stored at an optimal temperature between 20°C and 25°C. The degradation process, which involves oxidation, sulfonation, and inactivation by racemization to the dextroisomer, is accelerated by exposure of epinephrine solution to air, heat, and light. The degradation products, which include adrenochrome, melanin, L- or D-adrenaline sulfonate, and D-adrenaline, have little or no pharmacologic activity.[10]

Previously, we have determined that out-of-date autoinjectors might not provide an optimal dose of epinephrine, even if their contents appear to be clear and without apparent pink or brown discoloration from adrenochrome or melanin, respectively. Unused EpiPens and EpiPens Jr were studied 1 to 90 months after the expiration date stated on the autoinjector labels. The epinephrine content of the autoinjectors, measured by using a high-performance liquid chromatography UV technique,[8] correlated inversely with the length of time past the expiration date, and epinephrine bioavailability from the out-of-date autoinjectors was reduced significantly.[9]

In many countries worldwide, epinephrine autoinjectors remain unavailable or unaffordable for people who are at risk for anaphylaxis in the community.[5,6] Under these circumstances, physicians sometimes equip their patients with an ampule of epinephrine and a 1-mL syringe and needle; however, this potentially leads to delayed dosing, overdosing, or underdosing. In a previous study,[7] we found that people without health care training who were instructed in how to draw up a dose of epinephrine from an ampule took significantly longer to get the dose into the syringe than physician and nurse controls did; furthermore, the epinephrine content of the dose drawn up by laypeople ranged 40-fold, and their speed and accuracy did not correlate.

Where epinephrine autoinjectors are unavailable or unaffordable, physicians sometimes also equip their patients with unsealed, disposable plastic 1-mL syringes containing a premeasured dose of epinephrine in solution for use as first-aid treatment.[5,6] Here, for the first time, we report the stability of epinephrine solutions in unsealed syringes evaluated under different concurrent suboptimal storage conditions.

We determined that there was a gradual decline in the epinephrine dose remaining in the syringes stored at high temperature under conditions of both high and low humidity. The decline was significantly more rapid in the syringes stored at low humidity, suggesting that concerns about stability should be greatest when syringes containing epinephrine solution are stored in hot, dry environments. When the epinephrine dose was calculated as the percentage remaining in the solution and compared with the US Pharmacopeia compendial limits of 90% to 115%, it was only within compendial limits for 2 months in syringes stored under conditions of low humidity and for 3 months in syringes stored under conditions of high humidity. Contrary to what was expected, exposure to light under the conditions tested had no significant effect on the epinephrine dose remaining in the syringes after 5 months of storage at either high- or low-humidity conditions.

On the basis of these results, in hot climates, if an unsealed syringe prefilled with an epinephrine dose is provided for the first-aid treatment of anaphylaxis, it should be replaced every few months on a regular basis with a new syringe containing a fresh dose of epinephrine.

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