



Letter

Epinephrine doses contained in outdated epinephrine auto-injectors collected in a Florida allergy practice

Anaphylaxis guidelines recommend prompt injection of epinephrine (adrenaline) from an epinephrine auto-injector (EAI) as first-line treatment when anaphylaxis occurs out-of-hospital.¹ Patients at risk are instructed to carry their EAIs at all times and be prepared to use them when anaphylaxis occurs.¹

Manufacturers' storage recommendations for EAIs such as the EpiPen typically include keeping them at 20°C to 25°C (68°F to 77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F); protecting them from light; avoiding refrigeration or exposure to excessive cold or heat; and replacing them when the solution is discolored or contains a precipitate.²

Epinephrine auto-injectors such as the 0.3-mg EpiPen contain 2 mL of a sterile epinephrine solution (1 mg/mL), of which only 0.3 mL (0.3 mg) is ejected at activation. The epinephrine solution also contains 6 mg of sodium chloride, 1.67 mg of sodium metabisulfite, and hydrochloric acid to adjust the pH.²

With exposure to oxygen, light, or heat, epinephrine in solution degrades rapidly, resulting in pink or brown discoloration because of adrenochrome and melanin formation. Although patients are advised to replace their EAIs before the expiry date, outdated EAIs are sometimes kept on hand for backup use or because patients cannot afford timely replacements or ignore the need for replacements.³

Information has been published about out-of-hospital storage conditions for epinephrine^{4,5} and about the stability of different epinephrine formulations under various storage conditions, of which temperature range is most critical.^{4–10} For example, inside closed vehicles parked in sunlight, ambient temperatures can reach 80°C (176°F) and degradation of epinephrine solutions in multidose vials can occur.⁵

However, there is minimal published information about the stability of epinephrine in EAIs. In a study conducted in Albany, New York, where outdoor temperatures range from –9°C to 28°C (15°F to 82°F), outdated EAIs with expiry dates from 2002 through 2013, collected from ambulances, contained only 12.6% to 31.1% of the labeled epinephrine content.¹⁰ In a study conducted in Winnipeg, Canada, where outdoor temperatures range from –35°C to +35°C (–31°F to 95°F),³ outdated EAIs collected in exchange for within-date EAIs in a hospital allergy clinic and studied 1 to 90 months after their stated expiry dates contained 51% to 102% of the labeled epinephrine dose.³

The present study was designed to determine the epinephrine doses in outdated EAIs collected in an allergy practice and to test

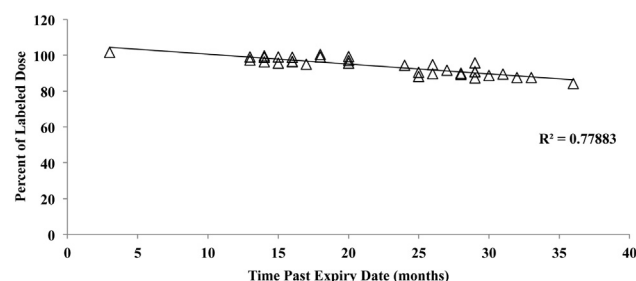


Figure 1. Percentage of labeled epinephrine dose from individual epinephrine auto-injectors vs time past expiry date.

the hypothesis that the dose would correlate inversely with the number of months past the expiry date stated on the label (the “labeled dose”). We measured the volume of epinephrine solution ejected at activation and the epinephrine concentration in the remaining solution and then calculated the epinephrine dose in each EAI.

Thirty-five EpiPens (0.3 mg, $n = 30$; 0.15 mg, $n = 5$), 3 to 36 months past the expiry date indicated on the label, were collected from patients in Florida, where outdoor temperatures range from 11°C to 32°C (53°F to 90°F). The specific storage conditions for each EAI were unknown but might have included purses, briefcases, pockets, fanny packs, backpacks, and vehicles. In the allergist's office, the EAIs were stored at room temperature.

The EpiPen activation mechanism was evaluated by pushing the orange tip firmly against a pre-weighed 15-mL collection tube, holding the activated EAI in place for 10 seconds until ejection was complete, and then reweighing the tube to determine the mass of the solution collected. Subsequently, the solution volume was determined gravimetrically and compared with the stated volume (0.3 mL) that should be ejected at activation.

Each activated EAI was opened and the epinephrine solution remaining (~1.7 mL) in the glass syringe inside was transferred into a 4-mL collection tube and inspected for discoloration and precipitates. Discoloration intensity was graded visually from 1 to 6 using a color scale (eFig 1).

The epinephrine concentration in the residual solution was analyzed using the official United States Pharmacopeia assay for epinephrine injection,¹¹ a reverse-phase high-performance liquid chromatographic method with ultraviolet detection at 280 nm (Waters Corporation, Milford, Massachusetts). The calibration curve at epinephrine concentrations of 6.125 to 600 $\mu\text{g/mL}$ was linear, with a correlation coefficient (R^2) of 0.9997. The epinephrine content (dose) was calculated by multiplying the concentration times the ejected volume.

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The EAls delivered a mean $\pm$ SD volume of 0.301 ± 0.007 mL (range 0.282–0.317 mL) that was not significantly different ($P < .05$) from the volume of 0.3 mL that should be delivered at activation. Of the 35 epinephrine solutions, 18 were very lightly discolored (color intensity code 5). None contained precipitates. Color intensity increased with the increasing number of months past the expiry date, with a correlation of 0.788 (eFig 2).

The percentage of labeled epinephrine dose calculated in the solutions from the EAls ranged from 84.2% to 101.5% and decreased with increasing number of months past the expiry date, with a correlation of 0.779 (Fig 1). However, all EAls that were no more than 24 months past the expiry date contained more than 90% of the labeled epinephrine dose and therefore met current United States Pharmacopeia standards of 90% to 115% of labeled doses. The EAls that were 24 to 36 months past the expiry date were very lightly discolored (color intensity code 5) and contained 84.2% to 95.7% of the labeled dose.

The color intensity of an epinephrine solution was not an accurate indicator of the epinephrine dose remaining, because some discolored solutions still contained the labeled dose, whereas others contained a lower dose because of epinephrine solution degradation. Enhanced stabilization of epinephrine solutions might extend the shelf-life of EAls. Paradoxically, decreasing the sodium metabisulfite content has been reported to improve the stability of the epinephrine solutions in EAls.⁷

In summary, we found that the epinephrine solutions in EAls that were no more than 24 months past the expiry date contained at least 90% of the labeled dose in the expected 0.3-mL volume, and although some were minimally discolored, none contained precipitates. Although no human studies of the biologic consequences of using outdated EAls have been published, in animal models, injection of epinephrine from outdated auto-injectors has been associated with decreased bioavailability³ and injection of degraded epinephrine has been associated with decreased biological activity.⁸

Therefore, patients should monitor the expiry dates of their EAls and replace the EAls as this date arrives. However, in the first-aid treatment of anaphylaxis, if the only EAI available is outdated but free of precipitate, it could be used in preference to no epinephrine injection at all, because it might still have some beneficial effects.³

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anaai.2015.01.015>.

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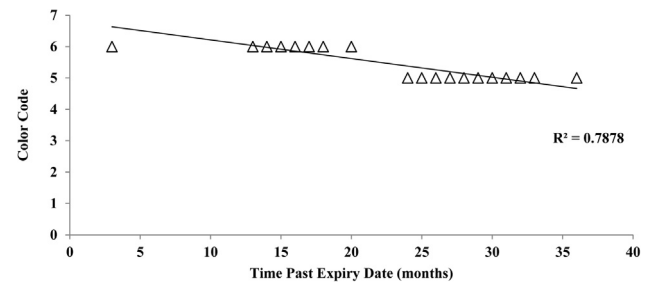
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Color Grade	Code
Very dark	1
Dark	2
Medium	3
Light	4
Very light	5
Clear	6

eFigure 1. Color grading and corresponding coding used in the discoloration intensity inspection.



eFigure 2. Discoloration intensity of solution of individual epinephrine auto-injectors vs time past expiry date.