Outdated EpiPen and EpiPen Jr autoinjectors: Past their prime?

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Background: EpiPen and EpiPen Jr autoinjectors are often recommended for prehospital treatment of anaphylaxis. When these units become outdated, there may be a delay in replacing them.
Objectives: Our purpose was to evaluate unused, outdated EpiPen and EpiPen Jr autoinjectors, obtained from patients at risk for anaphylaxis, for epinephrine bioavailability and epinephrine content.
Methods: We conducted a prospective, randomized, cross-over study of epinephrine bioavailability after injection from outdated autoinjectors in rabbits; controls included EpiPen and EpiPen Jr autoinjectors that had not expired ("in-date" autoinjectors) and intramuscular injection of 0.9% saline solution. In addition, the epinephrine content of the outdated EpiPen and EpiPen Jr autoinjectors was measured by a spectrophotometric method and an HPLC-UV method.
Results: Twenty-eight EpiPen and 6EpiPen Jr autoinjectors were studied 1 to 90 months after the stated expiration date. Most were not discolored and did not contain precipitates. Epinephrine bioavailability from the outdated EpiPen autoinjectors was significantly reduced ($P < .05$) compared with epinephrine bioavailability from the in-date autoinjectors. The inverse correlation between the decreased epinephrine content of the outdated autoinjectors, assessed with an HPLC-UV method, and the number of months past the expiration date was 0.63.
Conclusions: For prehospital treatment of anaphylaxis, we recommend the use of EpiPen and EpiPen Jr autoinjectors that are not outdated. If, however, the only autoinjector available is an outdated one, it could be used as long as no discoloration or precipitates are apparent because the potential benefit of using it is greater than the potential risk of a suboptimal epinephrine dose or of no epinephrine treatment at all. (J Allergy Clin Immunol 2000;105:1025-30.)

Key words: *Epinephrine, adrenaline, EpiPen, EpiPen Jr, autoinjector, anaphylaxis, allergic reaction, food/venom/latex allergy, adult, child*

Abbreviations used

AUC:	Area under the plasma epinephrine concentration versus time curve
C_{max}:	Maximum plasma epinephrine concentration
IM:	Intramuscular
t_{max}:	Time of maximum plasma epinephrine concentration
USP:	*United States Pharmacopeia*

Prompt injection of epinephrine is of fundamental importance in the treatment of systemic anaphylaxis.[1-4] For the prehospital treatment of anaphylaxis, epinephrine autoinjectors in the form of the EpiPen and the EpiPen Jr are commonly recommended because they provide the advantages of an easy-to-use, sterile, premeasured single dose. The total volume in each autoinjector is 2 mL, of which 0.3 mL is injected intramuscularly (IM) when the device is used correctly.[5,6] Each 0.3 mL in the EpiPen contains 0.3 mg of epinephrine, 1.8 mg of sodium chloride, 0.5 mg of sodium metabisulfite, and hydrochloric acid to adjust the pH to 2.2 to 5.0 in Water for Injection. Each 0.3 mL in the EpiPen Jr contains 0.15 mg of epinephrine and the same nonmedicinal ingredients in the same amounts as listed for the EpiPen.[5]

Epinephrine is an inherently unstable chemical.[7-10] In aqueous solution, even in the presence of sodium metabisulfite, it is susceptible to oxidation and inactivation by partial racemisation to the dextroisomer.[7] It degrades rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin.[5] Measures to prevent oxidative degradation of epinephrine include supplying it in an acidic solution containing an antioxidant and use of a light-resistant container. The pharmacologic activity and the potential toxicity of the epinephrine degradation products have not been optimally studied.

The information provided about the EpiPen and EpiPen Jr, including the information in the package inserts dispensed with the autoinjectors and the information appearing on the autoinjectors themselves, states "Store in a dark place at room temperature (15-30°C, 59-86°F). Do not refrigerate. Replace the auto-injector if the solution is discolored or contains a precipitate."[5,6] Although there is a high level of awareness of the expiration date on the autoinjectors,[11] many patients at risk for anaphylaxis carry EpiPens that are outdated.[12]

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We hypothesized that epinephrine would be present in an EpiPen or EpiPen Jr after the expiration date had passed but that the amount would correlate inversely with the number of months past this date. We tested this hypothesis by assessing the bioavailability of epinephrine from outdated EpiPen and EpiPen Jr autoinjectors in 6 rabbits with use of a prospective, controlled, randomized, cross-over study design. After each EpiPen and EpiPen Jr was used in the bioavailability study, the autoinjector was inspected for discoloration or precipitates and then opened for removal of the residual epinephrine solution, measurement of the epinephrine concentration in this solution, and calculation of the exact dose of epinephrine that would have been administered.

METHODS

Source of outdated EpiPen and EpiPen Jr autoinjectors

Advertisements posted in our allergy clinics during April and May 1999 invited patients at risk for anaphylaxis to bring in outdated unused EpiPen and EpiPen Jr autoinjectors and exchange them for in-date autoinjectors, which were purchased from a local pharmacy and supplied free of charge. In response, 28 outdated unused EpiPen autoinjectors and 6 outdated unused EpiPen Jr autoinjectors were turned in for use in this study. Patients, or if the patients were children, their caregivers, were asked the following questions about the outdated autoinjectors: (1) Did a physician and/or a pharmacist ever discuss the expiration date and optimal storage conditions with you? (2) Did you check the expiration date and appearance ("color window") of the autoinjector at regular intervals? (3) Where exactly was the autoinjector stored; specifically, had it ever been exposed to extreme heat or extreme cold? (4) Why did you keep the autoinjector after the expiration date had passed?

Six EpiPen autoinjectors (lot No. 8C6498, expiration date March 2001) and 5 EpiPen Jr autoinjectors (lot No. 8C5415, expiration date June 2000) (Allerex Laboratory, Kanata, Ontario, Canada) and 0.9% saline solution for IM injection were purchased from a local pharmacy for use as in-date controls.

Bioavailability of epinephrine from outdated EpiPen and EpiPen Jr autoinjectors

In 6 New Zealand White rabbits weighing 4.6 ± 0.2 kg, we performed a prospective, controlled, randomized, cross-over study of epinephrine bioavailability from the 28 outdated EpiPen and 6 outdated EpiPen Jr autoinjectors. The Animal Use Protocol was approved by the local Protocol Management and Review Committee of the University of Manitoba. The positive controls were 6 EpiPen and 5 EpiPen Jr autoinjectors that had not expired (in-date), and the negative control was IM injection of 0.9% saline solution. The bioavailability studies were conducted over an 8-month period, with a recovery time of 1 to 4 weeks between studies. On each study day 2-mL blood samples were collected into tubes containing EDTA before the epinephrine or saline solution injection, and at 5, 10, 15, 20, 30, 40, 60, 90, 120, and 180 minutes afterward. Samples were centrifuged at 4°C. Plasma was transferred into an appropriately labeled polypropylene tube with screw cap, frozen promptly in an upright position, and stored at –20°C until epinephrine concentrations were determined.

Measurement of plasma epinephrine concentrations by HPLC with electrochemical detection

Solid/liquid-phase extraction of thawed plasma samples was performed, with an efficiency of 75% to 80%. Epinephrine concentrations were measured with use of an HPLC reverse-phase system (Waters, Milford, Mass) with electrochemical detection. With this assay, it was possible to detect as little as 5 pg/mL (0.025 nmol/mL) of epinephrine.[13] Calibration curves were linear over the range 25 to 1000 pg (0.125-5 nmol/L) with a coefficient of variation of 3% at 1000 pg and 10% at 25 pg. By this method, epinephrine could be distinguished from its metabolites and degradation products and from sodium metabisulfite.

Epinephrine pharmacokinetic parameters were calculated from plasma epinephrine concentration versus time plots with standard pharmacokinetic equations and the computer program WinNonlin (Scientific Consulting, Apex, NC).

The maximum plasma epinephrine concentration (C_{max}), the time of maximum plasma epinephrine concentration (t_{max}), and the area under the plasma concentration versus time curve values were compared after the injection of the outdated and in-date EpiPen and EpiPen Jr autoinjectors and 0.9% saline solution, with PCSAS computer programs, ANOVA, and analysis of covariance. The C_{max} values were evaluated over time expired with linear regression analyses. Differences were considered to be significant at $P < .05$.[14]

Measurement of epinephrine content in outdated EpiPen and EpiPen Jr autoinjectors with two different analytic methods

At the conclusion of each bioavailability study, the EpiPen or EpiPen Jr autoinjector that had been used was saved for assessment of epinephrine content. Each autoinjector was closely inspected for discoloration or precipitates, after which the needle was carefully removed and the autoinjector itself was opened with a sharp knife. The glass vial inside contained a postinjection volume of approximately 1.7 mL epinephrine, sodium chloride, sodium metabisulfite, and hydrochloric acid.[5,6] This solution was frozen at –20°C and was later thawed and used for determination of epinephrine content by both a spectrophotometric method with detection at 530 nm and an HPLC method with UV detection at 280 nm.[15]

The epinephrine concentrations were measured in the residual solution obtained from the outdated and in-date control EpiPen and EpiPen Jr autoinjectors. The epinephrine content remaining was then calculated as percent of the dose indicated on the autoinjector label and plotted versus months elapsed since the expiration date indicated on each autoinjector. The data were analyzed with PCSAS and linear regression.[14]

RESULTS

Twenty-eight EpiPen autoinjectors and 6 EpiPen Jr autoinjectors were studied 1 to 90 months after the stated expiration date. One hundred percent of patients and caregivers recalled that the issues of expiration date and optimal storage conditions had been discussed with them, and 74.5% had checked the expiration date or appearance of the autoinjector at regular intervals. Reliable information regarding storage history was available for 78.6% of the EpiPen autoinjectors and for 100% of the EpiPen Jr autoinjectors. One EpiPen studied 1 month past the expiration date had been exposed intermittently to extreme temperatures (in the glove compartment of a car) for days at a time. The others had been kept in purses, briefcases, pockets, school bags, backpacks, fanny packs, cupboards, and drawers. Two EpiPen auto-injectors studied 20 and 51 months past their stated expiration date contained pinkish-brown discolored contents. None

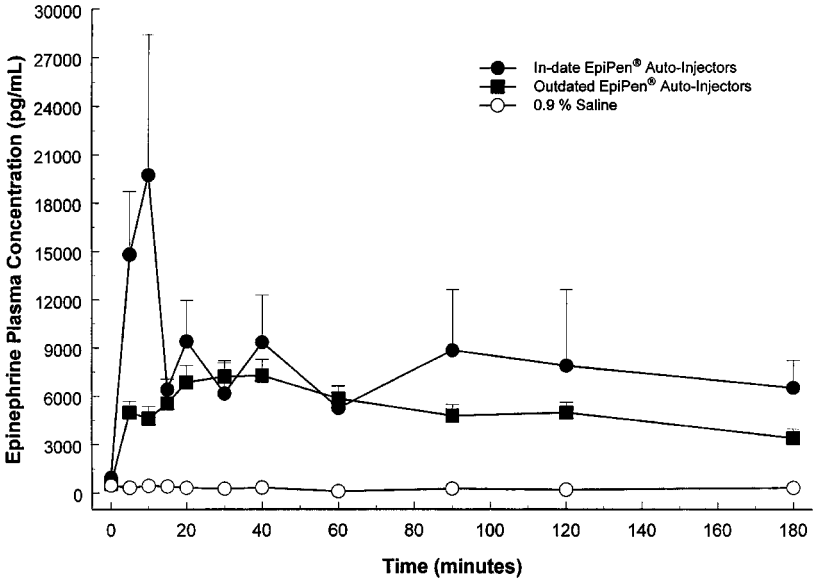

FIG 1. Epinephrine bioavailability from outdated EpiPen autoinjectors *(closed squares)* was significantly reduced ($P < .05$) compared with epinephrine bioavailability from in-date EpiPen autoinjectors *(closed circles).* Plasma concentrations of endogenous epinephrine measured after injection of the 0.9% saline solution control are represented by *open circles.*

TABLE IA. Epinephrine bioavailability from outdated EpiPen autoinjectors

Epinephrine bioavailability studies (mean ± SEM)	Outdated EpiPen HPLC-EC (n = 28)	In-date EpiPen (control) HPLC-EC (n = 6)	0.9% Saline solution (control) HPLC-EC (n = 6)
C_{max} (ng/mL)	10.8 ± 0.9*	26.2 ± 6.9	0.5 ± 0.1†
t_{max} (min)	33.6 ± 5.9	9.2 ± 2.4	–
AUC (μg/mL/min)	0.87 ± 0.09	1.42 ± 0.34	0.05 ± 0.02†

EC, Electron capture.
*$P < .05$ versus in-date.
†Endogenous epinephrine.

TABLE IB. Epinephrine bioavailability from outdated EpiPen Jr autoinjectors

Bioavailability studies (mean ± SEM)	Outdated EpiPen Jr (n = 6)	In-date EpiPen Jr (control) (n = 5)
C_{max} (ng/mL)	6.9 ± 1.1	9.2 ± 1.2
t_{max} (min)	34.2 ± 17.8	8 ± 2
AUC (μg/mL/min)	*	0.36 ± 0.04

*Invalid data because of delayed absorption.

appeared to contain precipitates. Most patients and caregivers turning in an unused, outdated autoinjector also had an in-date autoinjector available. Common reasons stated for keeping the outdated ones were "So I can teach someone how to give it," "Kept as back-up," "Forgot to throw it out," "Never throw anything out," and "Don't know why."

On inspection, most of the plastic sheaths containing the outdated autoinjectors were shabby or shattered, but all the autoinjectors themselves were intact and functioned as designed when the injections were given in the bioavailability study. Epinephrine bioavailability from the outdated EpiPen autoinjectiors was significantly reduced ($P < .05$) compared with epinephrine bioavailability from in-date EpiPen autoinjectors (Fig 1, Tables IA and IB); however, there was minimal correlation of C_{max} values with the number of months past the expiration date ($r = 0.23$). The bioavailability of epinephrine from the 2 discolored EpiPen autoinjectors and from the EpiPen that had been stored intermittently at extreme temperatures did not differ from that of other EpiPen autoinjectors that were outdated by a similar number of months.

By use of the United States Pharmacopeia (USP) spectrophotometric method, relatively high "epinephrine" concentrations were found in the outdated autoinjectors, probably because epinephrine degradation products, in

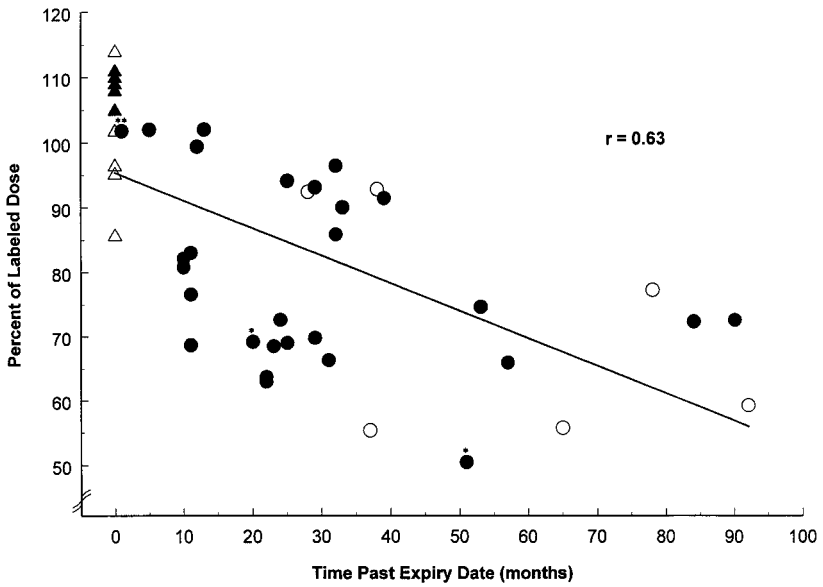

FIG 2. The epinephrine content, expressed as percent of labeled dose of epinephrine, of 6 in-date EpiPen autoinjectors *(closed triangles)* and 6 in-date EpiPen Jr autoinjectors *(open triangles)* is shown. The percent of labeled dose of epinephrine in 28 outdated EpiPen autoinjectors *(closed circles)* and 6 EpiPen Jr autoinjectors *(open circles)* studied 1 to 90 months after the stated expiration date correlated inversely with the number of months past the expiration date (0.63). The EpiPen autoinjectors with discolored contents are indicated with an *asterisk.* The EpiPen stored in the car glove compartment is indicated with *two asterisks.*

TABLE IIA. Epinephrine content of outdated EpiPen autoinjectors

Epinephrine content studies	Outdated EpiPen Spectrophotometric (n = 21)	Outdated EpiPen HPLC-UV (n = 28)	In-date EpiPen HPLC-UV (n = 6)
Epinephrine (mg)	0.295 ± 0.009	0.238 ± 0.008	0.326 ± 0.003
Percent ± SEM	99 ± 3	79 ± 3	109 ± 1
Percent range	52-113	51-102	105-111

TABLE IIB. Epinephrine content of outdated EpiPen Jr autoinjectors

Epinephrine content studies	Outdated EpiPen Jr Spectrophotometric (n = 6)	Outdated EpiPen Jr HPLC-UV (n = 6)	In-date EpiPen Jr HPLC-UV (n = 5)
Epinephrine (mg)	0.144 ± 0.008	0.108 ± 0.011	0.148 ± 0.007
Percent ± SEM	96 ± 5	72 ± 7	99 ± 5
Percent range	83-119	55-93	86-114

addition to epinephrine itself, reacted with the color-producing reagents (Tables IIA and IIB). In contrast, with the USP HPLC-UV method, in which the degradation products could be differentiated from epinephrine, the epinephrine content in the outdated EpiPen autoinjectors was found to be variable but generally lower than indicated on the label; the inverse correlation between the content and the number of months past the expiration date was 0.63 (Tables IIA and IIB, Fig 2). One EpiPen with discolored contents, 20 months past the expiration date, retained 66% of labeled strength; another, 51 months past the expiration date, retained 51% of labeled strength. The EpiPen stored intermittently in the car was 1 month past the expiration date and had 102% of labeled strength.

As measured with the USP HPLC-UV method, the in-date EpiPen autoinjectors had a mean ± SEM content of 109% ± 1% (range 105% to 111%) of labeled strength (Table IIA). The in-date EpiPen Jr autoinjectors had a mean ± SEM content of 99% ± 5% (range 86% to 114%) of labeled strength (Table IIB).

DISCUSSION

Physicians, pharmacists, and nurses are often asked about the importance of the expiration date on the EpiPen or EpiPen Jr autoinjectors and whether the autoinjectors can be used even if they are outdated. This study was performed to provide a practical answer to these questions

because there is no published information about the epinephrine bioavailability and the epinephrine content of outdated EpiPen and EpiPen Jr autoinjectors.

We found that epinephrine bioavailability from the outdated EpiPen and EpiPen Jr autoinjectors varied with the number of months past the expiration date but was significantly reduced compared with epinephrine bioavailability from the in-date autoinjectors. The epinephrine content of the autoinjectors could not be assessed accurately with the USP spectrophotometric method, which is primarily intended for use in quality control of epinephrine solutions during the manufacturing process.[15] The epinephrine content of the autoinjectors, as measured with an HPLC method with UV detection that distinguished between the parent compound and degradation products, correlated inversely with the number of months past the expiration date. Most of the EpiPen and EpiPen Jr autoinjectors that had a reduced epinephrine content could not have been identified by inspection of the color window on the autoinjectors for discoloration or precipitates.

The compendial limits for the epinephrine content of Epinephrine Injection are 90% to 115% of labeled strength.[15] To obtain the maximum shelf life possible, when unstable compounds such as epinephrine are manufactured in unit dosage forms, the formulations generally contain close to maximum compendial limits. From analysis of the in-date control EpiPen and EpiPen Jr autoinjectors, it appears as if this practice has been followed, with the longest shelf-life correlating with the highest epinephrine content. Epinephrine USP 1 mg/mL or 0.5 mg/mL solutions containing sodium metabisulfite are relatively resistant to degradation compared with more dilute solutions of epinephrine. Epinephrine is more prone to degradation in extreme heat than in extreme cold. Cyclic heating at 65°C for 8 hours per day for 4 to 12 weeks has been shown to result in approximately 30% reduction in epinephrine concentrations in epinephrine USP solution, with no visible discoloration as an indicator of the lack of integrity of the solution.[8-10]

The concept of an expiration date on foods, medications, and other products sold for human consumption or use is well accepted worldwide. Although there is evidence from this study and from a previous study[11] that patients at risk for anaphylaxis have a high awareness of the expiration date on the EpiPen autoinjector, there is also evidence that many such patients may be carrying out-of-date autoinjectors.[12] If an item is perceived as being costly and is seldom actually used, consumers may be tempted to delay in replacing it when it becomes outdated.

The patients and caregivers providing unused, outdated EpiPen and EpiPen Jr autoinjectors for this study had been instructed to avoid exposing the autoinjectors to temperature extremes and, for the most part, had not knowingly exposed the autoinjectors to unfavorable conditions. This is an important issue in our geographic area, where outdoor temperatures range from –35°C in winter to +35°C in summer. The results of the study may therefore be more favorable with regard to epinephrine bioavailability and content from outdated autoinjectors than if the autoinjectors had been obtained from people who had not been specifically instructed with regard to their optimal storage and had allowed them to be refrigerated, frozen, or, worse, to be exposed to high temperatures for sustained periods of time.

Failure to administer epinephrine promptly has been identified as the most important factor contributing to death in patients with anaphylaxis; nevertheless, even when epinephrine is given promptly, it is not always effective.[16,17] This has generally been attributed to the extremely rapid progression of some episodes of anaphylaxis, failure to administer epinephrine by a route that facilitates prompt absorption, failure to follow the instructions for epinephrine injection correctly, or failure to administer an adequate epinephrine dose.[16-18] In addition, patients taking β-adrenergic blockers may be resistant to the effect of epinephrine.[19] The possibility has also been raised that occasional patients with anaphylaxis may react adversely to sodium metabisulfite and may not get relief from injection of an epinephrine solution containing this preservative.[20] On the basis of the results of the study reported here, another potential reason that should be considered for apparent failure of epinephrine to relieve anaphylaxis symptoms is inadvertent administration of a suboptimal dose because of use of outdated epinephrine.

For prehospital self-management of anaphylaxis, we recommend the use of EpiPen and EpiPen Jr autoinjectors that have not expired. If, however, the only autoinjector available is an outdated one, it could be used so long as no discoloration or precipitates are apparent because the potential benefit of using it is greater than the potential risk of a suboptimal epinephrine dose or of no epinephrine treatment at all.

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