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Research Article

The Effects of Heating on EpiPen Epinephrine Auto-Injector Device Integrity and Function

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Abstract

Background: Temperatures above manufacturers' recommendations (20-25°C; excursions 15-30°C) can be encountered frequently. The dashboards of cars in the sun can exceed 85°C on a 37°C day.

Objective: To evaluate the integrity and function of EpiPens after being heating to high temperatures.

Methods: For 97 pars of same-dose, same-lot, post-consumer expired EpiPens (51 0.3mg and 46 0.15mg), one was heated in a 77°C oven then cooled to room temperature (heated-cooled), while the other was kept in usual conditions (control). Both were then activated, and the decrease in device mass was measured to estimate the amount of solution fired. Paired t-tests were used to determine if there was significant average difference in mass between heated-cooled devices and control devices. Regression models compared heated-cooled versus control device outcomes while adjusting for device dose (0.3mg vs. 0.15mg) and expiration date, with interaction terms. Malfunctioning devices were dissected and examined for damage.

Results: Heated-cooled devices lost less mass when firing, versus controls (0.275 vs. 0.283, paired t-test p-values <0.0074). The effect of heating did not differ after adjusting for dose or expiration date. Most (92%) of the EpiPens were difficult to remove from their carrier tubes, with visible melting around the top rim. Eight heated-cooled devices fired improperly (7) or failed to fire (1); none had damage or visible melting on dissection, but one had blackened liquid within. Controls all functioned normally.

Conclusion: Heating EpiPen devices to 77°C melted carrier tubes and impaired device function. Devices exposed to extreme heat should be replaced.

Keywords: Anaphylaxis; Auto injector; Auto-injector; Epinephrine; EpiPen; Temperature; Heat; Hot; Sun; Device; Function

INTRODUCTION

Epinephrine Auto Injectors (EAIs) are used to rapidly medicate and combat the dangers of anaphylaxis, a life threatening allergic reaction which needs immediate treatment with epinephrine to prevent serious adverse outcomes or death [1].

As patients with life-threatening allergies should carry EAIs with them routinely, it is easy for them to get left behind in vehicles. Sometimes this can result in EAIs being exposed to temperatures exceeding recommended ranges. Previous studies have shown that car dashboards can reach temperatures as high as 85°C (185°F) [2]. We aimed to determine the effects of prolonged heating on the function and integrity of EpiPen (0.3mg) and EpiPen Jr (0.15mg) devices.

METHODS

Our primary aim was to determine if EpiPen and EpiPen Jr. Devices exposed to high heat simulating car conditions on a hot day would fire normally. We hypothesized that a heated then cooled (heated-cooled) EpiPen will fire 10% less solution after having been heated and cooled than a paired control device. This was assessed by measuring the loss in mass during firing of heated-cooled and control devices, and comparing the differences between the pairs of devices. Our secondary aim was to determine whether or not the heated-cooled devices would be damaged.

Consumers (colleagues, patients and parents of children with allergies) were contacted via social media and asked to donate expired EpiPen devices for this study; 100 pairs of post-consumer

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epinephrine auto-injector devices (52 pairs of EpiPen and 48 pairs of EpiPen Jrs) were collected. Devices were paired by dose, lot number, expiration date, and consumer. An informal survey of members of a social media allergy group revealed that 99% of 304 respondents store their/their child's EpiPen in the device's supplied carrier tube, as recommended by the manufacturer [3]. The devices were thus heated in the carrier tubes. One of each pair, the heated-cooled device, was placed on a silicone baking mat pyramid over a metal tray, ensuring the devices were protected from direct metal contact (Figure 1). An Omega USB-1 Pro A high temperature data logger was also placed on the mat next to the devices, to record oven temperatures every 10 minutes during the 8-hour heating period. The other device of the pair, the "control", was stored in manufacturers' recommended conditions.

Figure 1: EpiPen devices and a temperature sensor being placed in the 77°C oven.

The heated-cooled devices were heated on the center shelf of a Wolf 30" Dual Fuel Range 4 Burner Cooktop Oven, a standard kitchen oven, set at 77°C (170°F), for 8 hours. They were heated in six groups, with approximately 18 EpiPens per round. They were cooled back to room temperature for a minimum of 24 hours prior to testing.

Heated-cooled and their paired control devices were then activated by firing them into a simulated limb (foam covered with a 1mm layer of rubber), and the devices were weighed pre-injection and post-injection using a Mettler Toledo analytical balance with accuracy to 0.001g. The difference between the pre and post-injection device masses were used to measure the mass of epinephrine solution fired.

The primary aim was assessed by comparing the change in device mass for heated-cooled devices with the change in device mass for paired control devices. Unadjusted analyses were performed using a paired t-test. Adjusted analyses were performed using generalized estimating equations which accounted for pairing and adjusted for device dose (0.15mg vs. 0.3mg) and expiration date (in months).

Difficulties removing the devices from their carrier tubes were categorized as: slipped out of the tube without assistance, needed to be pried out of the tube with fingers, or needed to be pried out of the tube with tools.

Carrier tubes and devices were inspected evidence of melting or other for damage. Any device that did not operate correctly was carefully opened by sawing through the three plastic projections on each side of the rear case that hold the plastic housing in place. All internal parts were then inspected for melting or damage. The syringe was inspected for cracks and the plunger was gently compressed to see if the seal was broken.

Based on data by Cooper et al., [4] we estimated that in a paired t-test, testing 22 pairs of devices would provide 90% power to detect a 5% difference in mean mass of an average control device between heated-cooled and control devices for both the meat and device outcomes. We set out to test 50 EpiPens and 50 EpiPen Jr devices to have sufficient power to evaluate each dose separately, as the epinephrine solution is diluted in the EpiPen Jr device and might respond differently to heat, and there is also one device component in an EpiPen Jr device that could react to heat which is not present in a 0.3 mg EpiPen device, a small black plastic sleeve that shortens the exposed needle length.

RESULTS

There were 100 pairs of devices prepared for study, but three pairs were removed due to technical difficulties with the analytical balance or missing data, and one device did not activate after heating: 96 devices (50 0.3 mg and 46 0.15 mg) had data for both devices of the pair and comprised the study sample.

After the oven reached an initial temperature of 77°C (170°F), the mean temperature over 8 hours was 85±1.7°C (185°F) with maximum of 90°C (194°F).

When the heated-cooled devices were removed from the oven, many of the carrier tube caps were noted to have popped open (Figure 2).

Figure 2: Heated-cooled devices after removal from the oven. Note that many of the carrier tube caps have partially opened during heating.

Ninety-two (91%) of the devices were difficult to remove from their carrier tubes: 90 needed to be pried out with fingers and two required pliers to remove. On external inspection, visible melting damage was evident on several carrier tubes, most notably on the ones that required pliers to remove the device (Figure 3).

Figure 3: visible melting of carrier tubes that were heated for 8 hours in an oven set at 77° C (top), compared with its carrier tube maintained at room temperature (bottom).

In unadjusted paired comparisons, heated-cooled devices lost less mass when firing, versus controls (0.275 vs 0.283, paired t-test p-values <0.0074), indicating that heated devices fired a smaller mass of epinephrine solution compared with their paired control device counterparts (Figure 4). After adjusting for solution type and expiration date, the results remained significant.

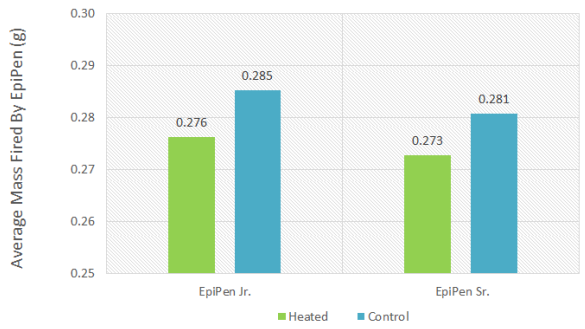

Figure 4: Average device mass lost by heated and cooled EpiPen 0.3mg and 0.15mg devices compared to their paired control counterparts.

Eight (8%) devices malfunctioned: three were difficult to activate requiring high activation forces and multiple attempts but eventually injecting the medication into the simulated limb; four devices didn't initially activate with pressure, then activated as the device was being lifted away from the limb, or as it was resting with no pressure being applied, thus not injecting medication into the limb; one device failed to activate despite repeated attempts, and the safety cap was difficult to reinsert. All control devices activated and released solution as expected.

The eight malfunctioning devices were sawed opened and examined. There was no evidence of melting, cracked vials or other damage. The rubber needle covers were in place. One device was noted to have a black liquid around the needle, grey rubber needle cover and orange shroud (Figure 5). This device uniquely lost very little mass during activation (change in mass 0.06mg). We surmise that most of the epinephrine solution was retained within the tip of device and left to interact with the rubber of the needle cover.

Figure 5: A device which activated late after attempted triggering, at a time when there was no pressure or contact. On opening hours later, black liquid was observed around the needle, rubber needle cover end.

DISCUSSION

Adhering to storage recommendations while always having a device immediately for use can be challenging, particularly for consumers who live in hot climates. EAIs are increasingly expensive, and replacing devices when exposed to temperatures outside of recommended ranges can cause not just inconvenience but also a financial burden for people with allergies [5]. Since mistakes happen, having good evidence when replacement is warranted for different exposures is important.

Patient information for EAIs marketed in the United States indicates that they should be stored between 20-25°C (67-77°F) with temporary excursions permitted in temperatures of 15-30°C (59-86°F) [6-8].Recommendations do not specify allowed excursion lengths, nor do they specify what to do if devices exceed allowed temperature ranges. The EpiPen FAQ section on the Mylan website and the provided patient information both advise EpiPen consumers not to refrigerate these devices, to avoid extreme heat, and to avoid storing them in the glove box of a vehicle [9].

Leaving EAIs in hot cars is particularly problematic because car temperatures can greatly exceed ambient temperatures. The maximum temperatures recorded in past studies were 85°C and 91°C, both dashboard temperatures [10].

Temperatures may vary considerably by location inside the car. Vanos evaluated final ambient car and surface temperatures, versus outside temperatures, for cars placed in sun versus shade. Maximum temperatures were reached on a 37.2°C day, and were ambient 48.9°C, dashboard surface 85°C and front seat surface 62.8°C. Similarly, Lacwik studied twelve 0.3mg EpiPens placed in three locations of a black sedan car: the glove compartment, the back shelf and the trunk [11]. The mean (maximum) temperature on the day of study was 27.3°C (32°C). The mean (maximum) temperature inside the car was: cabin 43.2°C (62°C), glove compartment 41.5 °C (53.1°C), trunk 37.5°C (49.0°C). Of concern, while the glove compartment temperatures didn't peak as high as ambient temperatures, this location did maintain a higher temperature longer during the day, and the 3 devices in this group had the lowest mean epinephrine concentrations compared with controls (0.26mg/0.3cm3 vs. 0.3mg/0.3cm3). Rudland compared temperatures in various locations (back shelf, seats, floors and trunk,) of a hatchback Ford Escort parked outside a clinic in Devon, England [12]. Temperatures were measured both inside a black medical bag, or in a shaded location beside the bag. The hottest temperatures of 80.2°C were reached on the car's back shelf, in the medical bag, and were 20°C hotter than the same location, shaded, just outside the bag.

Finally, an allergy blogger, Allergy Superheroes, studied 40 non-recalled expired EpiPen devices left in a dark blue compact car that was exposed to direct warm sun daily for 6 weeks [10]. She displayed 20 devices on the dashboard and stored 20 in the glove compartment. Measuring car temperatures with a Tempo Disc Bluetooth Wireless Thermometer, half-time in each location, the highest temperature reached on her dashboard was 90.8°C (195.4°F), and in her glove compartment was 58.7°C (137.7°F). She activated half of the devices while still hot, the other half after cooling. Similarly to our study, she noted that nearly half of the devices on the dash jammed, regardless of whether still hot. However, some of them activated late after she put them down. She did not note any problems with devices stored in the glove compartment.

Our study demonstrated numerous issues when devices were heated to temperatures similar to maximum temperatures reached in hot cars. The carrier tubes melted slightly, making the devices difficult to remove. Numerous devices failed to activate or had a long delay between triggering and releasing the needle and medication that would likely have meant the medication would

not have been delivered to the patient. The heated-cooled devices also fired statistically significantly smaller doses of epinephrine solution when compared to their unheated counterparts. For all of these reasons, in addition to the possible effects of heat on the epinephrine itself, [11] devices heated to these high temperatures are unsafe for use and should be replaced.

The problems removing the device were common and are important, even if the device itself is intact. EpiPens need to be readily available, and difficulties removing a device from its carrier tube during anaphylaxis could place a patient with allergies at risk. However, this problem could be easily tested and identified in advance simply by checking to see if the device slides out of the case easily after the heat exposure.

The problems with device malfunction were less common but more concerning. One possible explanation is that a plastic component melts slightly, too subtly to appreciate on visual inspection, but sufficiently to impair the triggering mechanism. Also concerning and for unclear reasons, devices that triggered did not deliver the same mass of epinephrine as their pair devices maintained at room temperature.

The overall differences in mass of drug fired were small but statistically significant. Given that expiration dates are based on ensuring a sufficient amount of drug remains available throughout the lifespan of the drug, these differences could be important in an allergic emergency.

While there are currently no simple solutions to the challenges of maintaining EAIs at room temperature, keeping devices protected from extreme temperatures is clearly important. Patient information should emphasize that devices cannot be left in cars or other small, enclosed environments such as storage units that are prone to high temperatures. Cases and/or device carriers such as the FRIO cooling case (Ready Care, LLC, Walnut Creek, CA) which modulate temperature should be better studied and if effective, covered by insurance plans. Manufacturers should better investigate whether devices could be stored refrigerated in very hot climates, as cooling has not been shown to degrade epinephrine or to alter the function of EpiPen devices [12,13]. More work should be done to develop heat-stable epinephrine for auto-injectors, such as the Andipen under development by Wind gap Medical, Inc. (Watertown, MA), where the medication is stored as a dry powder that is rapidly rehydrated when the cap is removed. Preclinical and animal model research involving microcrystal sublingual tablets of epinephrine suggest this may be a promising alternative to the use of an EAI, and would offer a simple and elegant solution to heat stability, while addressing a wealth of other issues [14,15].

CONCLUSION

In summary, heating EpiPen devices in their cases to temperatures comparable to what might be might be reached in a hot car with sun exposure results in heat damage to both the case and the device. After exposure to a mean of 85 degrees for eight hours, the device is likely to be difficult to remove from the case, may not activate properly, and even if it activates, the amount of epinephrine released may be reduced. An EpiPen exposed to significant heat can no longer be considered a safe and functional device and should be replaced.

CONFLICT OF INTEREST

None.

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REFERENCES

1. Boyce JA, Assa'ad A, Burks AW, Jones S M. Emergency department diagnosis and treatment of anaphylaxis: A practice parameter. Ann Allergy Asthma Immunol. 2014;113(6):599-608.
2. Vanos JK, Middel A, Poletti MN, Selover NJ. Evaluating the impact of solar radiation on pediatric heat balance within enclosed, hot vehicles. Temperature (Austin). 2018;5(3):276-92.
3. Mylan Specialty LP. Patient information: EpiPen, EpiPen jr 2020.
4. Cooper AQ, Qu P, Brown JC. The effects of freezing on epinephrine auto-injector device function. Ann Allergy Asthma Immunol. 2018;121(5):S57-S58.
5. Pepper AN, Westermann-Clark E, Lockey RF. The high cost of epinephrine autoinjectors and possible alternatives. J Allergy Clin Immunol Pract. 2017;5(3):665-8.e1.
6. kaleo. Auvi-Q, highlights of prescribing information, full prescribing information and patient information. 2020.
7. DailyMed. Epinephrine injection: Drug label information. Packager: Amneal pharmaceuticals of new York. LLC 2020.
8. DailyMed. Epinephrine injection: Drug label information. Packager: Teva pharmaceuticals USA, inc. 2020.
9. EpiPen. Frequently asked questions. 2020.
10. Allergy Superheroes. EpiPen glove box heat experiment. 2020.
11. Lacwik P, Bialas AJ, Wielanek M, Sklodowska M, Kupczyk M, Gorski P, et al. Single, short-time exposure to heat in a car during sunny day can decrease epinephrine concentration in autoinjectors: a real-life pilot study. J Allergy Clin Immunol Pract. 2019;7(4):1362-4.
12. Parish H.G., Bowser C.S., Morton J.R., Brown J.C. Visiting bags: A labile thermal environment. BMJ. 1994;308(6934):954-6.
13. Chow S-C, Shao J, Wang H. A systematic review of epinephrine degradation with exposure to excessive heat or cold. Ann Allergy Asthma. 2016;117(1):79-87.
14. Rachid O, Rawas-Qalaji M, Simons K.J. Epinephrine in anaphylaxis: Preclinical study of pharmacokinetics after sublingual administration of taste-masked tablets for potential pediatric use. Pharmaceutics. 2018 Feb 11;10(1):24
15. Rawas-Qalaji M.M, Werdy S, Rachid O, Simons F.E.R, Simons K.J. Sublingual diffusion of epinephrine microcrystals from rapidly disintegrating tablets for the potential first-aid treatment of anaphylaxis: In vitro and ex vivo study; sigma Aldrich. PharmSciTech. 2015;16(5):1203-12.