Epinephrine autoinjectors provide potentially life-saving therapy for pediatric and adult subjects with systemic allergic reactions, including anaphylaxis. However, the cost of these devices, specifically the EpiPen (Mylan, Canonsburg, Pa.), is increasing exponentially. Epinephrine autoinjectors are commonly prescribed in the United States but are not readily available worldwide. Alternatives for the self-administration of epinephrine exist and should be considered for patients who cannot afford or do not have access to these devices. The epinephrine prefilled syringe, stored in an eyeglass or pencil case, is a safe and viable option for the self-administration of epinephrine. Epinephrine prefilled syringes may not be as ideal as using autoinjectors but are superior to patients living without access to this medication. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017; : : :)

Key words: Epinephrine; Epinephrine autoinjectors; Anaphylaxis; Systemic allergic reaction; Cost; Price; Prefilled syringe; Ampule

INTRODUCTION AND COST OF EPINEPHRINE AUTOINJECTORS

Epinephrine is a potentially life-saving therapy for pediatric and adult subjects with systemic allergic reactions, including anaphylaxis.2-5 Epinephrine autoinjectors became available for patients in United States in 1980, with the introduction of the EpiPen (Mylan, Canonsburg, Pa.).3,4 The cost of these devices is increasing, despite the vital nature of autoinjectors and their availability in the United States for over 35 years.5 Costs were relatively stable, accounting for inflation, until Mylan acquired the EpiPen in 2007 from Merck (Kenilworth, NJ). Between 2007 and 2016, the average wholesale price of 2 EpiPens increased 54%, from $113.27 to $730.33.6 The exponential price increase persists even after accounting for inflation (Figure 1).6,7 The cost of epinephrine autoinjectors has become such an issue that the American Academy of Pediatrics Annual Leadership Forum included “Reducing the High Cost of Epinephrine Auto-Injectors” as one of their top 10 resolutions for 2016.8

EPINEPHRINE AUTOINJECTOR AWARENESS

The high price of epinephrine autoinjectors, specifically the EpiPen, is again a popular topic in the media. An online petition to investigate and regulate the price of the EpiPen has resulted in more than 140,000 letters sent to Congress.9 Senators have petitioned Mylan to decrease the price, with some success in the form of expanded patient assistance programs, savings card promotions, and plans to offer a less expensive, generic version of the EpiPen.10-12 Epinephrine autoinjector prescriptions are on the rise in the United States, with approximately a 70% increase in EpiPen prescriptions from 2003 to 2010, partially due to increased awareness about the need for autoinjectors.13 In addition, the US School Access to Emergency Epinephrine Act of 2013 incentivizes schools to stock epinephrine, and several state laws require schools to stock epinephrine.14 Many patients or parents purchase multiple epinephrine autoinjectors to keep at work, school, relatives’ houses, and on their person.15 Auto-injectors expire and must be replaced frequently. For subjects who do not have insurance or have insurance plans with high deductibles, the costs add up quickly.

EXISTING US EPINEPHRINE AUTOINJECTORS

All epinephrine autoinjectors are not created equal in regard to price or administration technique. As of October 2016, 2 epinephrine autoinjector devices are available on the US market, the EpiPen and the authorized generic of Adrenaclick, called the epinephrine injection, USP autoinjector (Lineage Therapeutics, Horsham, Pa).3,16,17 The brand named Adrenaclick was discontinued, according to representatives at Impax Laboratories (Hayward, Calif), the company that acquired Lineage Therapeutics and Amedra Pharmaceuticals (Horsham, Pa, the former manufacturer of Adrenaclick) in 2015 (Impax Laboratories representatives, oral communication, August 30, 2016).18 Reintroduction of the Auvi-Q (Kaléo, Richmond, Va) autoinjector is planned for 2017.19 Of the 2 available autoinjectors, the EpiPen is more familiar to patients, physicians, and the general public and is perceived as easier to use. The generic autoinjector is still expensive, with an average wholesale price of $494.01 for a 2-pack in 2015 and requires a different technique for use, with the removal of 2 caps, which may be more confusing to patients accustomed to the EpiPen.6,16 Epinephrine autoinjectors are rated “BX” by the US Food and Drug Administration, meaning “data that have been reviewed by the Agency are insufficient to
determine therapeutic equivalence" and may not be substituted for one another by a pharmacist.20,21

EPINEPHRINE AUTOINJECTOR AVAILABILITY AND ALTERNATIVES

The appeal of epinephrine autoinjectors is their convenience, stability, and ability to reliably administer a fixed dose of epinephrine, removing most human error. Epinephrine autoinjectors are commonly prescribed in the United States but are not readily available worldwide. In 2007, epinephrine autoinjectors for children and adults were available in 59.1% of 44 countries surveyed, based on responses from allergy/immunology specialists in the World Allergy Organization House of Delegates.22 However, even when obtainable, data on accessibility, based on costs and distribution, are not available. In other words, it is unknown how much of a given population in these countries can afford or have ready access to autoinjectors. Countries without access to autoinjectors use other methods for the self-administration of epinephrine.23 These alternative methods include ampules of epinephrine 1:1000 (1 mg/1 mL) with an empty syringe to be drawn up as needed and prefilled syringes containing epinephrine. Both options are less expensive than autoinjectors; a 1 mg/mL ampule of epinephrine (Hospira, Lake Forrest, Ill) has an average wholesale price of $2.52 and retail price of approximately $12.24 Both options also allow for tailored dosing of epinephrine, above or below the standard 0.15 mg or 0.3 mg dose provided by autoinjectors, which may be beneficial for children weighing less than 15 kg or obese and larger subjects.

Ampules of epinephrine with an empty syringe

The disadvantage of prescribing an epinephrine ampule with an empty syringe is that more skill is required to properly administer the medication in an emergency as compared with autoinjectors. Parents of patients with anaphylaxis take significantly longer to draw up epinephrine from an ampule (average 142 ± 13 seconds) as compared with emergency department nurses (29 ± 0.09 seconds) (P < .05).24 The epinephrine content of doses drawn up by parents also ranged 40-fold as compared with 2-fold for emergency department nurses.24 Therefore, the training required to draw up the correct dose of epinephrine from an ampule may be too complicated for many patients. Although the ampule and syringe is a less reliable method for epinephrine self-administration, it is an option for health care professionals. Institutions in Utah are supplying health care professionals with kits containing epinephrine syringes and ampules rather than autoinjectors to reduce costs.25

Prefilled syringes containing epinephrine

Because of concerns over the skill required to draw up the correct dose of epinephrine in an emergency, epinephrine pre-filled syringes (EPSs) are a more attractive option for subjects who cannot afford or do not have access to epinephrine autoinjectors. Indeed, the EPS is not a new concept. Before it was removed from the US market, the Ana-Kit (Hollister-Stier Laboratories, Spokane, Wash) contained a sterile syringe filled with 1 mL of epinephrine (enough for a repeat dose) housed in a protective case for subcutaneous injection.26,27 A new product, the Epinephrine Prefilled Syringe (Adams Pharmaceutical Corporation, San Diego, Calif), containing epinephrine 0.3 mg in a single dose syringe, is under review by and received a Complete Response Letter from the US Food and Drug Administration.28 Physicians may resort to prefilling syringes in clinic or asking pharmacists to fill syringes with the appropriate amount of epinephrine. However, concerns exist regarding the stability and sterility of EPSs because epinephrine degrades with exposure to ultraviolet light, oxygen in ambient air, and excessive heat.3,29,30 Epinephrine autoinjectors stored at 70°C for 10 days contained 62.6% ± 2.2% of labeled epinephrine concentration and delivered 77.7% ± 3.3% of labeled dose.30 The package insert for the EpiPen recommends storage at 20°C to 25°C with excursions permitted to 15°C to 30°C and protection from light using the carrier tube provided.31

EPSs stored at room temperature in a pencil box maintain acceptable US Pharmacopeia concentrations (90%-115% of label claim), pH, and sterility for 3 months.26 Even at higher than recommended temperatures, EPSs stored at 38°C maintain acceptable US Pharmacopeia concentrations for 3 months at high (95%) humidity and 2 months at low (15%) humidity.31 Epinephrine appears to be safe from degradation in colder temperatures that remain above freezing.29 Furthermore, EPSs can easily be protected from light by storing them in an eyeglass or pencil case. Although ultraviolet light degrades epinephrine, indoor light bulbs may not. One study found no difference in epinephrine concentrations in prefilled syringes stored in darkness or constant exposure to a 40-W light bulb after 5 months.31 Therefore, with proper precautions, EPSs appear to be stable, sterile, and safe for 3 months even in warmer climates. However, in climates with high temperatures and low humidity, the stability is limited to 2 months.23,31

Studies examining the safety and efficacy of self-administered EPSs for the treatment of anaphylaxis are not available in the literature. Randomized controlled trials examining the use of epinephrine administration by any route for the treatment of anaphylaxis in human subjects have not been done because of obvious ethical constraints. EPSs, filled the same day, are effective to treat systemic allergic reactions in the office setting.32 Other potential limitations include unintentional disconnection of the needle from the syringe, accidental needle pricks, or premature release of the medication. Safety concerns also exist for autoinjectors. Leg lacerations and accidental injections leading to digit ischemia are reported.33,34 Patients may also not be willing or able to administer an EPS to themselves or their children. However, the same is true for autoinjectors. Only 29% of parents administered EpiPens for recurrent anaphylactic reactions in their children.35

Education and teaching is required for the use of both EPSs and autoinjectors, although EPSs may require more training. Only 42% to 43% of patients are able to correctly administer autoinjectors 6 weeks after training according to the manufacturer’s instructions and a technique demonstration.36 Subjects can be taught to self-inject medication intramuscularly, as evidenced in the headache, arthritis, and contraception literature. Methotrexate and gold can be safely administered intramuscularly at home for treatment of rheumatoid or psoriatic arthritis.37 Two 20-minute training sessions, on average, were required to ensure proper
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