

Treatment of Anaphylaxis: Where is the Future?

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Anaphylaxis (anaphylactic shock) may follow an unexpected exposure of susceptible persons to an antigen such as food, medication, latex, insect venom, or other triggers in community settings [1-5]. The incidence of anaphylaxis is increasing each year, and fatalities, although preventable, still occur because of airway obstruction or vascular collapse [6,7].

For the emergency treatment of anaphylaxis, prompt intramuscular injection of epinephrine in the thigh muscle is the drug of choice. 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 [1-5]. Epinephrine auto-injectors such as EpiPen[®], EpiPen Jr[®] (Mylan, Inc., Basking Ridge, NJ), Twinject 0.3 mg[®], and Twinject 0.15[®] (Shionogi Pharma, Inc., Atlanta, GA) are commonly prescribed as the only available dosage form for the emergency treatment of anaphylaxis in a community setting. Mylan, Inc., which sells the EpiPen[®] auto-injector brand, they reported that they had maintained a 91% global market share and a 96% share in the U.S. auto-injector business in 2010, which amounted to roughly \$300 million in sales.

Despite being the only available dosage form for the treatment of anaphylaxis in community settings, epinephrine auto-injectors for self-injection are underutilized when anaphylaxis occurs due to several drawbacks [8,9]. Some of these drawbacks include: high cost which limits affordability and availability worldwide [9]; perceived large size and bulkiness; limitations on repeat dosing (if required) [10]; fear and anxiety associated with the use of needles [4]; and dosing errors due to incorrect technique of administration [7,11]. In addition, it is impossible to give an accurate dose to infants and to many children using currently available auto-injectors, which provide only two different premeasured, fixed epinephrine doses, 0.15 mg and 0.3 mg [4]. On the other hand, alternatives to an epinephrine auto-injector, such as an epinephrine ampule/syringe/needle or an epinephrine metered dose inhaler are impractical with regard to rapid and accurate dosing [4,12,13].

Furthermore, epinephrine in solution is inherently unstable. Degradation occurs gradually over time, even in the presence of an anti-oxidant such as sodium metabisulfite, and even if the solution is stored at an optimal temperature between 15°C and 25°C. The shelf-life of epinephrine solution contained in auto-injectors is limited to 12-18 months. The degradation process, which involves oxidation, sulfonation, and inactivation by racemization to the dextro-isomer, is accelerated by exposure of epinephrine solution to air, heat, and light [14].

Interestingly, almost all the dosage form developments achieved so far for epinephrine were related to the injectable dosage forms. Previously, Mylan, Inc. introduced their EpiPen 2 PAK[®] twin package to offer a second epinephrine dose similar to Twinject[®] and they enhanced their needle mechanism to be protected from exposure before and after EpiPen[®] use. Recently, Auvi-Q[™] by Intelliject, Inc. was approved by FDA in August 2012, which was licensed in 2009 to Sanofi-Aventis. Auvi-Q[™] is also an injectable dosage form, however, offers discreet rectangular size (3.5×2.0×0.5 inch) auto-injector with

voice instructions for patient or caregiver that is more compact to be fitted in the patient's pocket similar to a small wallet.

Therefore, there is increased interest in developing alternative novel, non-invasive epinephrine dosage form that provides epinephrine plasma concentrations equivalent to those obtained by epinephrine auto-injectors, available in a range of doses, have a long shelf-life, and be free from needle anxiety, the possibility of administration error, unintentional injection and injury.

The sublingual route is a promising alternative route for epinephrine administration. Drugs that can be absorbed sublingually bypass potential metabolic conversion in the gastrointestinal tract and hepatic first-pass metabolism, and reach the systemic circulation in a pharmacologically active form [15-17] epinephrine is extensively metabolized after oral administration by the catechol-O-methyltransferase in the gastrointestinal tract and by monoamine oxidase in the gastrointestinal tract and in the liver [18]. The high vascularity of the sublingual mucosa and the low molecular weight of epinephrine facilitate its rapid absorption directly into the venous circulation through the sublingual and frenular veins.

Recently, epinephrine was formulated into rapidly-disintegrating, taste-masked, and stable tablets that retain sufficient hardness to withstand shipping and handling and disintegrate to release epinephrine rapidly (≤ 30 sec) [19-23]. A 40 mg epinephrine dose administered sublingually was found to be bioequivalent to the adult dose of epinephrine IM injection, 0.3 mg, in a validated rabbit model [24-26]. This high sublingual dose was essential to create the required concentration gradient that promotes epinephrine absorption across the sublingual membrane and results in therapeutic plasma drug concentrations.

These rapidly-disintegrating sublingual epinephrine tablets may have the potential as user-friendly, non-invasive alternative for the first-aid emergency treatment of anaphylaxis in community settings.

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