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Emerging Therapies in Anaphylaxis: Alternatives to Intramuscular Administration of Epinephrine

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Abstract

Purpose of Review Anaphylaxis is a severe, life-threatening, systemic allergic reaction that should be recognized and treated promptly. Intramuscular (IM) epinephrine is the first-line treatment for anaphylaxis and there are no absolute contraindications to its use. Despite its established track record of efficacy and safety, physicians and patients face barriers in the recognition and treatment of anaphylaxis, including the maintenance and appropriate use of epinephrine auto-injectors. This has led to investigation into potential alternatives to IM epinephrine administration in anaphylaxis.

Recent Findings This review investigates the current standard of care in the treatment of anaphylaxis, barriers to IM epinephrine use, and alternative therapies under investigation for administration in anaphylaxis. Alternative routes under investigation include intranasal, sublingual, inhaled, and needle-free intramuscular administration of epinephrine.

Summary There are currently numerous investigational alternatives to IM epinephrine therapy which could hold promise as future effective treatments in the emergent management of anaphylaxis.

Keywords Anaphylaxis · Epinephrine · Epinephrine auto injector · Intramuscular alternative · Allergy

Introduction: Current Standard of Care in Anaphylaxis

Anaphylaxis is a severe, life-threatening, systemic allergic reaction that should be treated promptly. The treatment of choice for anaphylaxis is epinephrine, delivered intramuscularly (IM), which has been recognized as a safe and effective treatment for many years based on animal models, clinical pharmacology, and extensive clinical observation [1]. There are other adjunctive therapies that can be used in conjunction with IM epinephrine such as antihistamines, glucocorticoids, albuterol, intravenous fluids, vasopressors, and oxygen. However, IM epinephrine remains the definitive and only first-line medication in the treatment of anaphylaxis recommended in anaphylaxis consensus guidelines [2].

Anaphylaxis typically results from an overwhelming IgE response to an introduced allergen, with an estimated lifetime prevalence of 0.05-2% [3]. Anaphylaxis can result in a wide variety of symptoms and is best defined based on the clinical criteria depicted in Fig. 1 [4–8].

During anaphylaxis, vasoactive amines such as histamine and tryptase are released from mast cells and basophils. These immune mediators act on numerous end organs, including smooth muscle cells, small blood vessels, mucous glands, platelets, sensory nerve endings, and eosinophils. This can result in hypotension, vasodilation, bronchoconstriction, hyper-secretion from glands, smooth muscle contraction, neurotransmitter excitation, and edema. Epinephrine acts quickly as an agonist to alpha 1, beta 1, and beta 2 adrenergic receptors to reverse these adverse physiologic sequelae and prevent further mediator release [9]. At the doses used in anaphylaxis, epinephrine's alpha-mediated effects lead to vasoconstriction, increased peripheral vascular resistance, and decreased mucosal edema which alleviates hypotension, erythema, urticaria, and angioedema. The beta-mediated effects increase

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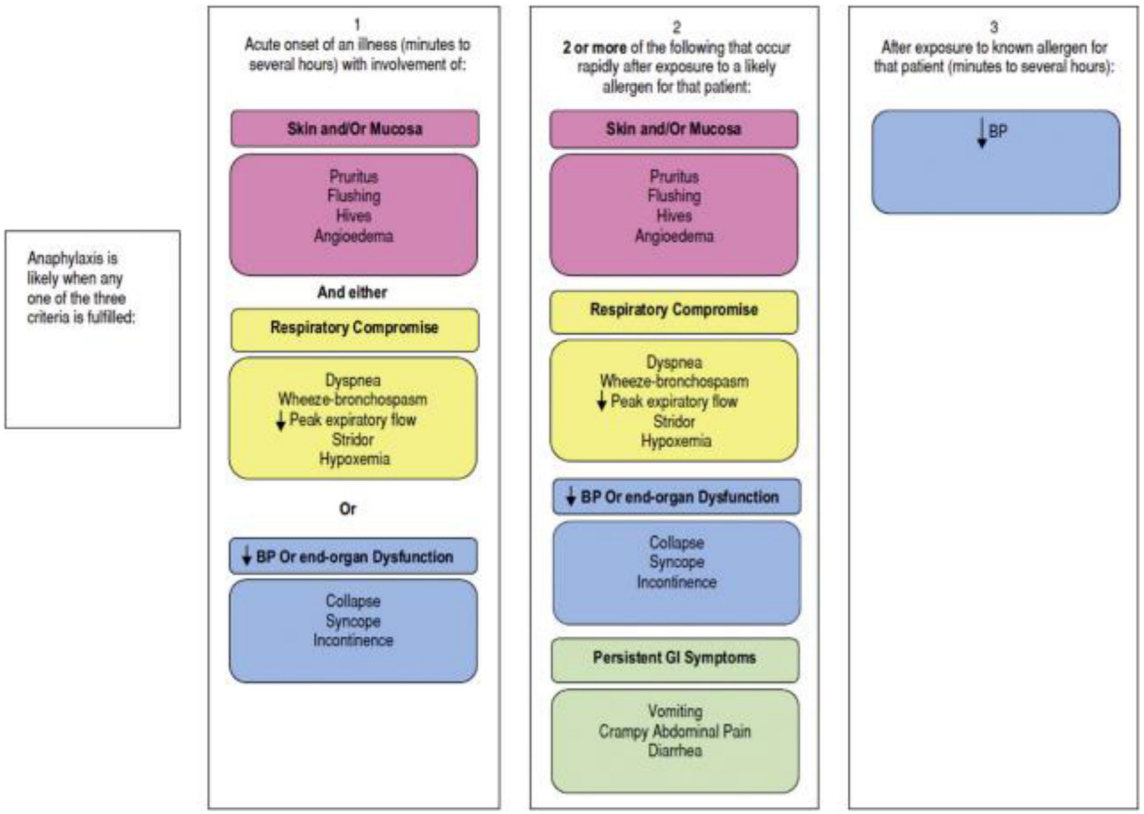

Fig. 1 Anaphylaxis criteria. Reprinted from Annals of Allergy, Asthma & Immunology with permission from Elsevier and from open access International Journal of Emergency Medicine

myocardial contractility, improve coronary blood flow, and pulmonary bronchodilation improving cardiac output and reversing bronchoconstriction [10]. Epinephrine also leads to activation of adenylate cyclase and cyclic adenosine monophosphate which inhibits further release of mast cell and basophil contents [9].

Once anaphylaxis is suspected, IM epinephrine should be rapidly administered in the lateral thigh. When administered intramuscularly, more rapid and higher peak plasma epinephrine levels are achieved as compared with subcutaneous (SC) administration in children or adults [11, 12]. The dosing of epinephrine in the treatment of anaphylaxis is 0.01 mg/kg of 1 mg/mL concentration with a maximum dose of 0.3 mg in younger children and 0.5 mg in adolescents and adults given every 5 minutes as indicated. Epinephrine auto-injectors (EAIs) are available for self-administration in pre-filled doses for out-of-hospital anaphylaxis treatment. There are no absolute contraindications to epinephrine use in the treatment of anaphylaxis and serious adverse effects are rare with appropriately dosed IM epinephrine administration [2]. Intramuscular administration is up to 10 times safer when compared to IV bolus administration, which has been associated with an increased risk of adverse events [13].

In outcome studies, early use of IM epinephrine has been shown to decrease need for subsequent doses, decrease hospitalizations, and decrease risk of fatality [8, 14]. To prevent delays to treatment, clinical criteria have been created to assist in medical provider's recognition of anaphylaxis, while emergency action plans are recommended to assist patients at home [15]. Despite these tools to aid in anaphylaxis diagnosis and management as well as the known safety and efficacy of IM epinephrine, there are still significant barriers to the prompt and appropriate treatment of anaphylaxis with IM epinephrine. These barriers include few options for dose and needle length in the currently marketed auto-injectors, low EAI prescription rates, under-utilization of auto-injectors in anaphylaxis, inadequate training leading to needle injury and needle phobia, and the high cost and difficulty maintaining supplies.

Challenges with Current Standard of Care/Barriers to IM Administration

Challenges with current EAIs include appropriate dosing and EAI needle length at age and weight extremes. EAIs are the cornerstone of anaphylaxis treatment in the community and are available in 0.1 mg, 0.15 mg, and 0.3 mg doses for weight 7.5-15 kg, 15-30 kg, >30 kg respectively. These fixed doses often necessitate less-than-ideal dosing choices with higher

doses in young infants, lower than ideal dosing of patients in-between weight ranges as they approach the next dose range, and possibly lower than optimal dosing of very large patients who might be better managed with a dose of 0.5 mg. The recommendations found in the package inserts often do not reflect actual dosing choices made in practice. For example, since the 0.1 mg device is only made by one manufacturer, children <15 kg are often prescribed a higher than ideal dose. Furthermore, many pediatric and allergy organizations recommend switching to the 0.3 mg autoinjector at 25 kg to avoid inadequate dosing. Similarly, needle sizes may not be ideal for all users. Infants may be at risk of receiving an injection into periosteum or bone while individuals with a larger body habitus may be at risk of subcutaneous rather than intramuscular delivery depending on device needle length. Studies measuring skin-to-muscle depth and skin-to-bone depth using pressure and ultrasound have shown that children <15 kg risk injection into bone and children >30 kg risk injection into subcutaneous tissue [16, 17].

Low prescription rates of EAIs are another barrier to prompt treatment of anaphylaxis. Studies performed across different healthcare settings demonstrate low prescription rates without a clear explanation, although it may not be limited to concerns specifically about IM administration. One panel of emergency medicine physicians listed iatrogenic epinephrine overdose as a main barrier to use in the ED especially when the facility lacks auto-injectors, while difficulty determining risk for future reactions was listed as a reason not to prescribe an EAI [18]. In a cross-sectional study of pediatric Medicaid patients presenting to two pediatric emergency departments in the USA, only 64% of anaphylaxis patients received prescriptions for an EAI. Of those that were discharged at one site with prescriptions, 86% were filled by patients suggesting intervention should be targeted at the provider level [19]. Lower EAI prescription rates are described in other studies. One retrospective cohort in the USA reported that only 16% were prescribed an EAI within 60 days of the initial encounter while another Turkish study found only 10% of anaphylaxis encounters were prescribed an EAI [20, 21]. Similarly, in a retrospective review of patient visits to their primary care physician for allergy-related complaints, only 37% of high-risk patients were prescribed an EAI [22].

Even when patients are adequately prescribed an EAI, there is evidence that its use is highly under-utilized in the community and pre-hospital settings. There are multiple studies available that show that patients and providers are not comfortable with the use of an EAI, do not fully understand how to use it or the indications for use, and/or do not routinely have an EAI available for use during anaphylaxis. This is particularly concerning given that delayed use of epinephrine is associated with increased morbidity and mortality [23]. In terms of carriage rates, in a survey sent to patients with allergies, 89% reported filling a prescription for an EAI, however, just over half reported having access to their EAI in the event of an anaphylactic reaction [24]. Other studies have shown similar carriage rates and adolescents in particular listed inconvenience of carriage including size of device, perceived low likelihood of allergen presence, fear of needles, and attitudes of friends as reasons not to carry their EAI [25–28].

Carriage itself is not sufficient to ensure EAI use in anaphylaxis. In the community, patients and caregivers require training in order to be competent to use their auto-injectors. With different designs of epinephrine auto-injectors available in the USA, each with unique patient instructions, everyone caring for an allergic patient must be competent to use their auto-injector during an allergic reaction. In a study of preschool children with known food allergy, only 30% of severe allergic reactions were treated with epinephrine [29]. Another study involving allergic preschool children assessed teacher's baseline knowledge about prevalence of allergies in children, risk of anaphylaxis, attitudes on preparedness to deliver IM epinephrine, and practical delivery of rescue medications. Of 75 teachers, 63% were familiar with allergies, 11% felt well prepared for an anaphylactic reaction, 47% would administer an EAI in the correct clinical context, and only 17% were familiar with an EAI [30]. Under-utilization is not limited to this age group, and many studies have shown deficiencies in this regard among school age children as well as adolescents. In one study reviewing 245 participants who had experienced anaphylaxis, only 16% had received epinephrine. In this cohort, 54% felt EAI use was unnecessary, 19% were unsure if it was necessary, 8% had called EMS, 2.5% were too scared, 2.5% were not trained, 1.5% were en route to an ED, and 1% had an out-of-date device [31]. Even when EMS is involved, the use of IM epinephrine can still be optimized. In a retrospective review of children presenting to the pediatric ED with anaphylaxis, only 36% received epinephrine by pre-hospital providers prior to arrival and those who did not receive epinephrine were significantly less likely to be discharged home from that ED visit [32].

Needle phobia or fear of harming the patient may be a barrier to the use of IM epinephrine in anaphylaxis [28, 31, 33]. This phobia coupled with inadequate EAI training increases risk for accidental digital injection and other needle injuries by both patients and healthcare providers. Case reports and reviews have shown injuries such as leg lacerations, embedded needles, hooked needles, digit lacerations, and unintentional injection to bone [34–37]. Opportunities for frequent adequate training reviewing indication for EAI use, technique, and adequate hold for young children may alleviate some of this fear and reduce injury.

In addition to the practical issues and knowledge gaps mentioned above, there are also logistical barriers to the use of IM epinephrine. High cost of EAIs is certainly a commonly listed barrier to use. Between 2007 and 2016, the average wholesale price of two EpiPen® autoinjectors increased 545%, from

$113.27 to $730.33 [38]. In addition to price, in 2018, the FDA issued a supply shortage alert for EAIs. To combat this shortage, the FDA extended the expiration date on certain lots of 0.3 mg EAIs by 4 months. With high prices and difficulty obtaining supplies from pharmacies, many patients are forced to carry out-of-date EAIs. In a survey of adults with peanut allergy, 44% reported carrying expired devices with 25% being expired >3 months [39]. In terms of availability, a survey sent to pharmacies across the USA found that the average time to expiration of devices in stock was 11 months with the shortest time to expiration at 1 month. No pharmacy had EAIs in stock with the fully recommended 18 months until expiration time frame [40].

Clearly there are both physician and patient barriers to the prescription, maintenance of unexpired medication supply, and self-administration of IM epinephrine. Given these challenges, alternatives to IM injection have been sought to address many of these issues and merit further consideration. This review provides an overview of current alternatives to intramuscular therapy in anaphylaxis.

Alternatives to IM Therapy Under Investigation

Intranasal Epinephrine

Intranasal (IN) administration of epinephrine could be an effective alternative to IM given the vascularization of the nasal cavity which provides rapid onset action by bypassing first pass metabolism. It might also be more acceptable to patients as it avoids the emotional trauma associated with needle use. Atomizers, shown in Fig. 2, are frequently used for IN introduction of medication as they improve the volume of drug delivered, prevent run off, and optimize surface area for absorption.

In general, there are minimal side effects to nasal delivery and few contraindications (facial trauma, epistaxis, diseases with impaired ciliary function, e.g., cystic fibrosis). Due to slower absorption than the IM or IV route, a higher IN dose may be necessary to achieve adequate plasma concentration. Other types of rescue medications can be effectively administered IN, including IN midazolam in seizure rescue, IN naloxone in opiate overdose, and IN fentanyl in initial pain control [41].

Previous animal studies suggest that IN epinephrine is absorbable to the systemic circulation [42, 43]. In a study of the pharmacokinetics of IN epinephrine dosing in dogs, escalating doses of IN epinephrine were compared to IM administration. Escalating doses of IN epinephrine (2, 3, 4, 5, 10, and 20 mg) were administered and plasma samples measuring maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), and area under the curve (AUC 0-90min) were collected pre- and post-epinephrine delivery. This was compared to typical IM doses of either 0.15 mg or 0.3 mg. There were no significant differences in Cmax, Tmax, or AUC when the samples of 2 mg IN and 0.15mg IM dose were compared. Similarly, there were no significant differences in Cmax, Tmax, or AUC when samples of the 4 mg or 5 mg IN doses were compared to the 0.3 mg dose. However, there was a statistically greater average plasma concentration of epinephrine found for the 5 mg IN dose as compared to the 0.3 mg IM dose at 1 min after injection. No sustained adverse effects were noted for any of the IN or IM doses. The authors concluded that further clinical studies were warranted due to the potential benefits of IN administration including greater plasma concentration at 1 min (with similar other parameters), decreased risk of tachycardia, and convenient administration method [44].

Multiple human studies have further demonstrated that IN epinephrine effectively raises plasma epinephrine levels similarly to IM epinephrine. In a preliminary study of IN epinephrine administration, 5 healthy adult volunteers were administered IN saline as a negative control, IM 0.3 mg epinephrine as a positive control, and IN spray containing epinephrine bitartrate at 0.3, 0.6, 1.25, 2.5, and 5 mg. Each subject had blood drawn pre- and post-medication administration measuring plasma epinephrine concentration and the AUC at 0-120 min. For IN epinephrine, statistically significantly greater plasma epinephrine concentrations were observed for the 5 mg IN epinephrine dose as compared to the IN saline dose. Additionally, the plasma epinephrine concentration and time to reach maximum concentration of the 5 mg IN dose was comparable to the 0.3 mg IM dose. No serious adverse effects were observed for any dose [45]. Additionally, three recent studies have shown preliminary promise in the bioequivalence of IN epinephrine compared to IM epinephrine [46••, 47••, 48••]. The first study evaluated a 1 mg IN spray, 0.3 mg and 0.5 mg IM injection, and a subcutaneous injection of epinephrine in 36 subjects. The AUC for IN spray showed bioequivalence to 0.3 mg IM injection and showed more rapid absorption based on time to maximum concentration with favorable hemodynamic response. The second study was a crossover performed in 70 subjects receiving 1 mg IN, 0.3 mg IM, or 0.5 mg IM. Intranasal administration was again found to be bioequivalent; IN was absorbed faster compared to the 0.3 mg IM with higher peak concentration, but lower peak concentration compared to the 0.5 mg IM dose. Intranasal spray again showed a favorable hemodynamic response. The third study evaluated 1 mg IN spray compared to 0.3 mg IM administration in 36 subjects. Intranasal spray was again bioequivalent with faster absorption. No adverse effects were noted with the nasal administration.

It is important to note that these studies were all performed in healthy volunteers; thus, results of plasma concentration may be different in states of anaphylaxis. Additionally, there may be concern that histamine release in anaphylaxis may

Fig. 2 Atomizer for intranasal drug delivery

result in edema and swelling to the nasal mucosa, potentially impeding IN epinephrine absorption. To investigate this concern, dogs were administered IN histamine or IN saline followed by IN epinephrine. Increased nasal pressure was demonstrated following IN histamine administration. IN epinephrine was subsequently delivered and epinephrine plasma concentrations, Tmax, and AUC were measured. There was no difference in maximum epinephrine concentration or AUC between IN histamine and IN saline, and in fact, the time to max concentration was significantly less in the IN histamine group suggesting faster epinephrine absorption with histamine release [49]. Further human trials will be important in validating these findings; nevertheless, the aforementioned studies show promise of IN epinephrine spray as an alternative to IM therapy in anaphylaxis.

Sublingual Epinephrine

Sublingual administration of epinephrine is another potential route under investigation and requires absorption via the buccal mucosa in order to reach the bloodstream. This allows medications to bypass first pass metabolism of the liver, often making them faster than the oral route. This route of administration has proven effective for cardiovascular medications such as nitroglycerine and anti-nausea medications such as ondansetron.

In a prospective randomized cross-over study in animal models to evaluate sublingual epinephrine, rabbits received either 2.5 mg or 10 mg sublingual epinephrine tablets, 0.3 mg IM epinephrine, or 0.9% normal saline IM. Blood samples were obtained pre and post medication and sampled for Cmax and Tmax. This animal model showed that the plasma concentration and time to maximum concentration did not significantly differ between the 10 mg sublingual dose and the IM dose [50]. To further investigate sublingual dosing, another prospective randomized cross-over study was performed in which each rabbit was given either 10 mg, 20 mg, or 40 mg sublingual epinephrine tablets, a placebo tablet for negative control, and IM 0.3 mg epinephrine as a positive control. This study showed that the bioavailability of sublingual epinephrine increased with increasing dosage. Of the study doses, only the 40 mg sublingual epinephrine dose yielded no differences in the Cmax, Tmax, and AUC when compared to the IM dose [51].

Given the relatively high sublingual dosage required to create an optimal concentration gradient for sublingual absorption, researchers postulated that decreasing epinephrine particle size would increase absorption and allow a smaller sublingual dose to achieve adequate plasma concentration. A rapidly disintegrating sublingual tablet would allow for smaller dosing and would be more shelf stable than intramuscular epinephrine, up to 7 years [52]. To investigate this theory, another prospective placebo controlled randomized crossover study was performed in which rabbits received microcrystal sublingual epinephrine tablets in 20 mg or 40 mg doses, IM 0.3 mg and placebo. These microcrystal rapidly disintegrating sublingual tablets resulted in similar AUC, Cmax, and Tmax for the 20 mg sublingual dose compared with the IM 0.3 mg epinephrine. This formulation also allowed for a 50% dose

reduction while maintaining similar plasma concentration to IM dosage [53••, 54]. Using this data, the authors speculated that they could potentially use a rapidly disintegrating 30 mg sublingual tablet rather than the 0.15 mg IM dose of epinephrine in the treatment of pediatric anaphylaxis. A taste-masked tablet was developed to help with the intrinsic bitter taste of epinephrine and improve compliance in its future use. In this study, plasma epinephrine concentration, Tmax, and AUC were measured for the 30 mg sublingual tablet, 0.15 mg IM injection, and a placebo tablet. When compared to 0.15 mg IM, the 30 mg epinephrine sublingual tablet showed similar plasma concentration and time to this concentration, but showed significantly lower AUC. As such, further studies are needed to determine dose equivalence to the 0.15 mg IM dose [55].

These animal studies show the potential for sublingual epinephrine to maintain bioequivalent plasma epinephrine concentration, Tmax, and AUC as compared to IM administration. However, all studies thus far have been limited to animal models. In August 2020, the FDA fast tracked a phase 1 clinical trial of an epinephrine sublingual film which would deliver systemic epinephrine in anaphylaxis. This trial will enroll 28 healthy volunteers and will compare pharmacokinetics and pharmacodynamics of the sublingual film (AQST-108), 0.3 mg subcutaneous epinephrine, 0.3 mg IM epinephrine, and 0.5 mg subcutaneous epinephrine [56, 57]. It will be important to see how the sublingual route compares to IM administration in human clinical trials as well as during states of anaphylaxis as oral and sublingual mucosal swelling in anaphylaxis may affect the rate and extent of epinephrine absorption.

Inhaled Epinephrine

Inhaled epinephrine would be an appealing alternative to IM epinephrine therapy, if equally effective, and has been utilized in other clinical settings. Inhaled racemic epinephrine is routinely used in children in the hospital setting for the treatment of croup and a low-dose L-epinephrine inhaler recently received FDA approval for over-the-counter use in mild intermittent asthma for children >12 and adults.

A review of the literature published in 2009 assessed the utility of adding epinephrine inhalers in emergency kits for patients with anaphylaxis. Based on prior studies that noted no change in plasma epinephrine levels after 10 inhalations (0.15 mg per puff), shorter duration of action after 20 inhalations as well as increased gastrointestinal side effects, there was no compelling data to add aerosolized epinephrine to the emergency kits. Issues with inhaled epinephrine include poor delivery to the lungs and less absorption with most inhaled epinephrine ending up in the oropharynx and broken down by the GI tract. The authors concluded that patients would need to follow particular inhalation techniques and use 15-45 puffs to reach plasma levels comparable to 0.3 mg IM epinephrine [58]. However, due to ongoing reluctance of patients to use injectable epinephrine, a prospective randomized placebo-controlled trial in children with history of anaphylaxis was undertaken to study whether inhaled epinephrine could be a suitable alternative. Children were randomized to receive either inhaled epinephrine (0.25 mg) or placebo. Given the dose dependent nature of inhaled epinephrine and rapid absorption, inhaled epinephrine was dosed by body weight (10 inhalations for 20-30 kg, 15 inhalations for 30-40 kg, and 20 inhalations for >40 kg). On average, children were able to complete 11 inhalations or 74% of the calculated dose. Most children complained of the taste and experienced coughing and dizziness. Findings from this study suggest that the potential benefit of inhaled epinephrine was outweighed by the lack of feasibility of administering an adequate dose in the event of anaphylaxis [59].

Two additional studies attempted to evaluate the pharmacokinetic and dynamic profiles of inhaled epinephrine. These studies evaluated 4 mg and 8 mg doses of inhaled epinephrine compared with both 0.3 mg of IM epinephrine and placebo. Tmax was highest for the 8 mg dose with a lot of variability among individuals for the inhaled bioavailability. In addition, although the absorption was quick, the offset was also quick which may preclude a therapeutic effect in the event of anaphylaxis [60, 61].

Given the need for high doses and number of inhalations, the need for compliant administration, and reported side effects, inhaled epinephrine does not seem technically feasible or pharmacokinetically optimal for the treatment of anaphylaxis with the current technology.

Novel Approaches to the Traditional IM Device

Other research has sought to address issues with the IM delivery of epinephrine including ease of use for patients, portability, and shelf life with novel devices. For example, Windgap medical is in pilot production to commercialize a wet/dry autoinjector, ANDIPen®. Although this would not address all of the barriers related to IM delivery mentioned above, shelf-stability and supply shortages would be improved [62]. Finally, the most recent investigational alternative to IM auto-injectors is a needle-free intramuscular device. The ZENEO® auto-injector is a prefilled single use needle-free device currently under development [63]. The device propels medication at high enough speed and pressure to penetrate skin and deliver the medication intramuscularly. This device was tested in a prospective single center study in healthy adults who received an injection of saline to evaluate the functionality of the device in delivering medications intramuscularly. Ninety-five percent of patients had MRIs that demonstrated intramuscular delivery with a mean depth of 30 mm [64••]. Success with the ZENEO® device has been

reported with bioequivalence studies for injectable methotrexate levels in rheumatoid arthritis [65]. A needle-free, easy to carry device could improve utilization in anaphylaxis as it would alleviate patient and parental needle phobia and may simplify training. The company is currently working on making the device shelf-stable will potentially be available at the end of 2021 [66].

Conclusions and Recommendations

Consensus guidelines recommend IM epinephrine as the only first-line therapy in the acute management of anaphylaxis, with many adjunctive therapies also available. Even though delayed treatment of epinephrine is associated with increased morbidity and mortality, there are numerous barriers to the prescription, proper and timely administration of IM epinephrine, and adequate supply of EAIs. Investigational therapies are currently being evaluated that show promise as improvements or alternatives to IM epinephrine in the treatment of anaphylaxis. This review has highlighted three alternative routes to IM epinephrine delivery (IN, sublingual, inhaled), and two novel devices (an IM device with a potentially improved means of epinephrine storage, and a needle-free IM device). Of the alternative route therapies, intranasal and sublingual epinephrines have been most widely studied and show the greatest promise. The convenient delivery, bioequivalence, and favorable side effect profile of IN epinephrine make it an interesting alternative to IM epinephrine. While initial research is promising, more human studies will be necessary to see how absorption may be affected due to mucosal edema in anaphylactic states and in patients with mucosal edema from upper respiratory infections or allergies. The sublingual tablet has similar advantages and disadvantages, although taste may be an additional barrier, and more information is necessary to determine bioequivalence, particularly for the 0.15 mg IM dose. Further studies are underway. Inhaled epinephrine does not appear to be a viable alternative with current technology given the need for multiple inhalations, unclear delivery to the lungs, and unfavorable side effect profile. In the meantime, continued efforts to improve IM devices may decrease the hesitation surrounding epinephrine injection and thereby make a huge impact on the treatment of patients with anaphylaxis. The exciting research for alternatives to IM therapy that can match the pharmacokinetics and pharmacodynamics while maintaining a favorable side effect profile is ongoing. Hopefully, the field is getting closer to providing patients with an optimal management strategy that will promptly and effectively treat anaphylaxis in the community.

Declarations

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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