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Review Article

Epinephrine: A Review of Current Understanding and Future Direction

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Abstract

Introduction: The administration of injectable epinephrine is a widely utilized mechanism which has been employed as a lifesaving medication for decades. Despite the prevalence of this treatment technique, certain situations and patient populations necessitate a replacement for the epinephrine auto injector (EAI). There are several disadvantages of traditional EAIs. These drawbacks include high cost, short shelf life, low carry rate, difficulty to use or train with, fear of needles, fixed dosages, and fixed needle length. The most promising EAI alternatives include sublingual tablets and intranasal spray. These delivery methods have similar pharmacological effectiveness to EAIs with the benefits of modifiable dosages, high stability, and simplified administration. This review aims to evaluate deficiencies in implementation of the currently used EAI, investigate newly developed alternative delivery methods, identify gaps in the current literature, and suggest possible future studies.

Keywords: ***Autoinjector, epinephrine, intranasal, replacement, sublingual.***

1. Introduction

Epinephrine, also known as adrenaline, is an endogenously produced hormone and a medication. Epinephrine is a catecholamine which is synthesized from tyrosine in the chromaffin cells of the adrenal medulla [1]. The adrenal medulla is innervated by the splanchnic nerve and requires glucocorticoid stimulation to induce noradrenaline N-methyltransferase, an enzyme that converts norepinephrine into epinephrine [2]. The newly synthesized epinephrine is stored with adenosine triphosphate (ATP), calcium ions, and other proteins in chromaffin granules within the adrenal gland [3]. Sympathetic nerve activation results in splanchnic nerve stimulation. This stimulation results in an increase in acetylcholine and calcium entry into the chromaffin cells of the adrenal gland. This depolarization then results in secretion of epinephrine into the bloodstream via exocytosis [4]. The release of this hormone into the bloodstream results in activation of the sympathetic nervous system receptors.

1.1 Epinephrine Uses

The current approved uses for epinephrine include type-I hypersensitivity reactions (anaphylaxis), maintenance of mydriasis in intraocular surgery, and the treatment of hypotension resulting from septic shock [5]. In terms of incidence, the United States population experiences approximately 84,000 anaphylaxis cases annually, resulting in 840 fatalities per year [6]. Lifetime anaphylaxis prevalence for the United States population ranges between 0.05 and 2% [7], with rates steadily increasing over time [8].

As a medication, epinephrine is a life-saving compound that is mostly used when suspecting anaphylaxis. In 1968, Coombs and Gel originally classified anaphylaxis as an IgE dependent immune reaction [9]. However, there is no current universal clinical definition for anaphylaxis, and this condition may present with a wide array of symptoms [10]. Although this hypersensitivity reaction has varied mechanisms, presentation, and severity, it usually involves release of mast cell and basophil mediators with diffuse erythema, pruritis, urticaria, angioedema, bronchospasm, laryngeal edema, hyperperistalsis, hypotension, cardiac arrhythmias, nausea, vomiting, lightheadedness, and/or unconsciousness [11], as seen in Fig 1. Mast cells and basophils release tryptase, histamine, chymase, heparin, leukotriene B4, platelet activating factor, and other cytokines that result in anaphylactic symptoms [12], as seen in Fig 1. Approximately 92% of patients in an 835 subject retrospective series

experienced generalized urticarial and angioedema as the most common symptoms of anaphylaxis [13-15]. Anaphylaxis can also cause shock by critically effecting the bronchial smooth muscle, resulting in bronchospasm and loss of airway, right ventricular heart failure, and pulmonary vasoconstriction. Furthermore, these shock symptoms can result in hypoxia and rapid death if untreated [16,17].

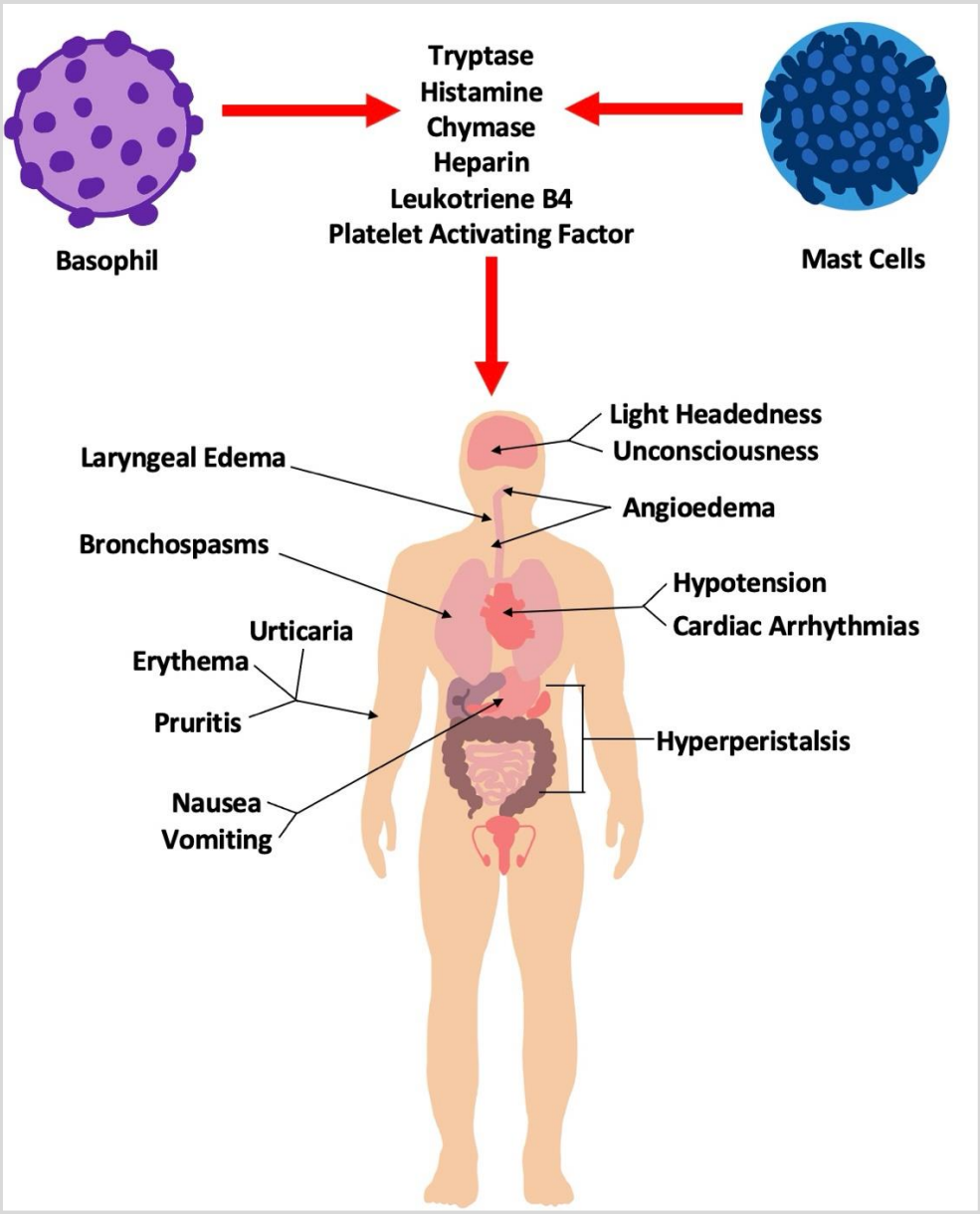

Fig 1. Causes and Symptoms of Anaphylactic Shock (color use)

Anaphylaxis has been demonstrated to follow activation of basophils and mast cells that result in the production and secretion of tryptase, histamine, chymase, heparin, leukotriene B4, and platelet activating factor [12]. These mediators result in a variety of systemic symptoms including lightheadedness, unconsciousness, laryngeal edema, angioedema, bronchospasms, hypotension, cardiac arrhythmias, urticaria, erythema, pruritis, hyperperistalsis, nausea, and vomiting [11].

1.2 Epinephrine Mechanism of Action

Epinephrine has many diffuse tissue targets to block the progression of an allergic response. Its' use produces rapid reactions to the eyes, skin, heart, skeletal muscles, liver, and airway to produce fight-or-flight reactions. Off label uses of epinephrine injection include ventricular fibrillation, pulseless ventricular tachycardia, asystole, pulseless electrical activity, croup, and severe asthma exacerbations[18].

Epinephrine exerts lifesaving effects by acting upon the β and α adrenergic receptors, as shown in Fig 2. At low doses, epinephrine preferentially targets β receptors (especially β1). At high doses, epinephrine's effects are primarily mediated through the α1 receptor [19]. β1 receptors predominate in the heart and cerebral cortex, while β2 receptors predominate in the airway and cerebellum. Both β1 and β2 receptors are found in the heart and brain [20]. β1 increases sinoatrial and atrioventricular nodal firings as well as ventricular contraction, resulting in a positive chronotropic and inotropic response. β1 receptors also increase renin release from kidneys, resulting in an increase in blood volume via angiotensin 2 and aldosterone [21]. In addition, β2 activation results in airway smooth muscle relaxation, uterine relaxation, and modulation of immune system effects [22]. α1 receptor activation increases the amount of intracellular calcium, resulting in smooth muscle contraction and glycogenolysis [23]. Also, α2 receptor decreases intracellular calcium to decrease neurotransmitter release and vasodilation [23]. Epinephrine administration is not without risks. Tachyarrhythmia, digital ischemia, and hypoperfusion may potentially arise during use of any epinephrine administration [19].

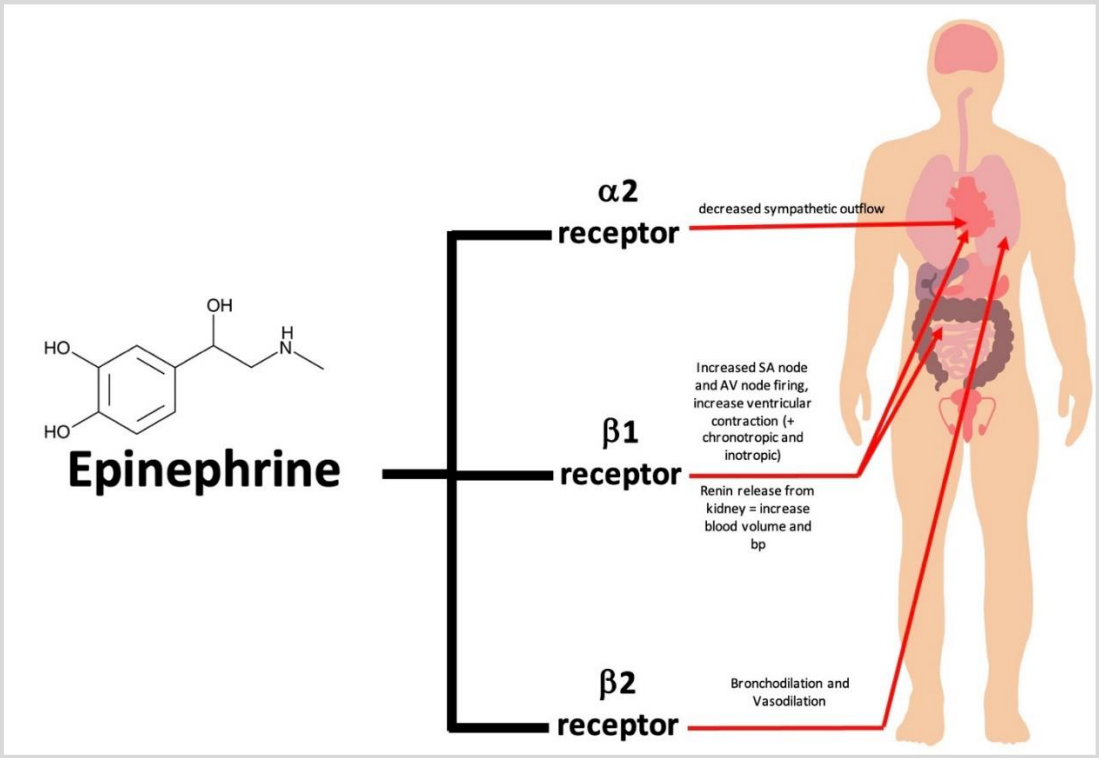

Fig 2. Effects of Epinephrine in Treating Anaphylaxis (color use)

Epinephrine has been consistently shown to modulate bodily function and immune responses through the activation of adrenergic receptors. Activated α2 receptors result in decreased sympathetic tone of cardiac muscle [23]. Activated β1 receptors result in an increased chronotropic effect on the pacemaker cells of the heart and an increased inotropic effect on the myocytes of cardiac ventricles. β1 stimulation also results in the release of renin from the kidney, which functions to increase blood volume and pressure [21]. Activated β2 receptors stimulate bronchodilation and vasodilation in the lungs and pulmonary system [22].

1.3 Current Standard of Care

The current standard of care for administration of epinephrine is a rapid intramuscular injection into the lateral thigh [24]. Current EAIs reach a peak plasma concentration in five to ten minutes, and effectiveness depends on the skin to muscle depth ratio of the injection site [25]. The skin to muscle depth ratio varies inversely with absorption and time to peak plasma concentration [26]. Meta analyses of epinephrine use demonstrate that the rapid deployment of intramuscular epinephrine significantly decreased need for subsequent dosing, hospitalizations, and risk of fatality [27]. Delayed use of EAIs can contribute to exacerbation of symptoms, severe anaphylaxis, and even death. Significant barriers to EAI use include cost, shortages, and education on delivery methods [28]. Rising costs prevent access for many patients who could benefit from at home access to EAIs. Brand name EAI costs rose from $113.27 to $730.33 between 2007 and 2016 [29]. This cost barrier is even more significant for certain EAI brands [30]. Shortages of these medical devices have also impacted prescription and use. One study found that EAIs are only prescribed to 16.2% of patients diagnosed with anaphylaxis [31]. This lack of availability may contribute to increased risk of severe anaphylaxis and life-threatening complications.

2. Alternative Epinephrine Delivery Methods

2.1 Drawbacks of EAIs

There are several disadvantages of the currently used EAI mechanism of drug delivery, as shown in Fig 3. Many children and family members do not have access to proper instruction about the use of EAI [32]. A survey of child and adolescents found that 54% of patients experiencing anaphylaxis did not use EAI because they were unsure if it was necessary, while only 17% of subjects experiencing anaphylaxis successfully used EAI [33]. In addition, further studies concluded that 56% of parents with anaphylactic children are hesitant in using the EAI due to a fear of hurting the child or causing a bad outcome [34]. To further complicate use of this drug with children, there is not an ideal dosage option for pediatrics. Fixed EAI dosages of 0.1 mg, 0.15mg, and 0.3 mg do not optimally correspond to many ages and sizes of children. Furthermore, a fixed needle size and length significantly increases the risk of injection into periosteum or bone in children [35,36]. Pediatric anaphylaxis cases have drastically increased in the last decade [37]. This documented increase highlights the need for an epinephrine administration technique that is safe, easy to use, and economical for pediatric patients and their families.

There are many severe consequences which may result from the delayed use of epinephrine in anaphylaxis due to fear of needles [38]. Fear of adverse effects also impacts epinephrine use [39]. In addition, surveys have shown a rare complication of EAI use can result in laceration or embedded needles. Older models of EAIs are associated with significantly higher adverse events, including digital injection [40]. The use of EAIs is further complicated by short shelf lives and the need to purchase new devices nearly every year. EAIs have a shelf life of 12 to 18 months, even when stored in optimal conditions [41]. The short window of EAI effectiveness results in a higher economic burden for patients and their families. The recurrent cost of EAIs that must be purchased approximately once a year could contribute to delayed use or lack of an available EAI. In patients with a prescription for an EAI, only 44% reported carrying EAI "all the time" [42]. The decision to not consistently carry an EAI could be impacted by cost, convenience, size of device, or improper training. Further research into this topic is required to determine if an alternative epinephrine administration device could improve patient quality of life and outcomes.

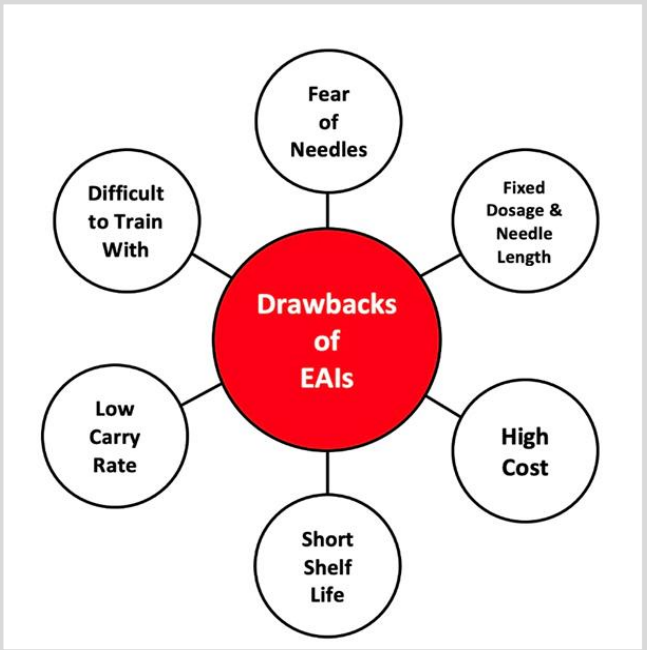

Fig. 3 Drawbacks of Current EAI Devices

Current epinephrine delivery devices have several mechanistic weaknesses including difficulty for patients and caregivers to train with [32,33], less than optimal carry rates due to bulkiness and design [42], relatively short half-life [41], high cost of nearly annual prescriptions [29], fixed dosages and needle lengths not conducive to pediatric populations [35,36], and delay or refusal to administer based on fear on needles [34,38].

2.2 Sublingual Epinephrine Administration

Given that self-injectors are underused for a variety of reasons, other alternatives are being explored to improve the management of anaphylaxis. These alternatives avoid the use of needles, are easier to use and train with, and are theorized to be safer with less adverse events. Clinically meaningful blood concentrations can be obtained by sublingual epinephrine which dissolves on contact with the oral mucosa. Epinephrine is a lipophilic drug with a low molecular weight that is most likely absorbed across sublingual mucosa into venous circulation by transcellular diffusion [43]. Sublingual epinephrine tablets have no significant difference in maximum plasma concentration and time to maximum plasma concentration as compared to traditional EAIs [44]. Sublingual epinephrine has very similar pharmacokinetics to EAI that have been replicated in multiple studies [45,46]. From a peak blood concentration standpoint, sublingual administration bypasses portal circulation and potential metabolism in the gastrointestinal tract and hepatic first pass metabolism [47]. These pharmacokinetic and pharmacodynamic aspects make sublingual epinephrine administration an attractive choice to replace EAIs, especially in pediatric and other special patient populations that may be averse to needles.

Oral-mucosal products are versatile alternatives, especially for geriatric, pediatric, and non-compliant patients due to needle-free ease and convenience of use [48]. Rawas-Qalaji, Simon, & Simons, prominent researchers in the field of sublingual epinephrine replacement, recommend 54.58 mg of epinephrine bitartrate in a taste-masked rapidly dissolving sublingual tablet (RDST) to treat pediatric anaphylaxis [49]. Also, RDSTs were found to remain stable through shipping and may retain activity for up to 7 years, even in less than optimal storage conditions [50]. The high stability of sublingual epinephrine formulations is in stark contrast to traditional EAI preparations that have been shown in some studies to lose efficacy as quickly as 12 months after production [41]. Further evaluations of anaphylactic response as well as cost analyses are needed.

2.3 Nasal Epinephrine Administration

Nasally introduced epinephrine is another promising alternative to the traditional EAI. Nasal administration is noninvasive, has a fast onset of relief, and bypasses first past hepatic metabolism [51]. Hemodynamic measurements may be bioequivalent or possibly faster than injectable doses. One adult human model showed significant systemic absorption of epinephrine via intranasal (IN) route at 5 mg. This IN dosage was observed to have similar area under curve and time to maximum as the traditional EAI. This model suggests that a 5 mg dose is required via the IN route to achieve the same effects as an EAI intramuscular (IM) administration of 0.3 mg [52]. IN epinephrine has similar sympathetic effects to intravenous (IV) epinephrine in a canine CPR model [53], suggesting that IN epinephrine may be used to treat anaphylaxis in a comparable manner to traditional EAIs.

IN drug administration is widely used in emergency settings, with examples including lorazepam, fentanyl, naloxone, haloperidol, and midazolam. IN administration may even be more convenient for healthcare providers than traditional EAIs [54]. Health care providers have expressed a preference for nasal spray over EAIs [55]. However, IN administration is contraindicated if a patient has facial trauma, epistaxis, or impaired ciliary function [24]. These factors make IN epinephrine a promising area of research that may eventually replace EAIs in acute care situations. Further consumer cost and shelf-life studies are needed to determine the viability of widespread prescription and distribution.

3. Conclusion

Multiple disadvantages of traditional EAIs include high cost, short shelf life, low carry rate, difficulty with use and training, fear of needles, fixed dosages, and fixed needle length. Certain populations, including pediatrics, may benefit from a noninvasive route of epinephrine administration where the dosage can be easily modified to the needs of the patient. Preliminary and animal studies have shown favorable pharmacology profiles for both sublingual and IN epinephrine administration. One downside of these alternatives is that both administration techniques require significantly higher dose preparations of epinephrine to elicit comparable responses to EAIs. A current gap in understanding exists in terms of patient and provider preferences, pharmacokinetics in a large and diverse patient population, long term safety profile, and ease of use in acute settings. Further research is also needed to determine the relative cost and logistics of transitioning to new models of epinephrine administration. The development of safe and effective EAI alternatives may revolutionize treatment of anaphylaxis in life threatening situations. The development of alternative routes of administration may prevent significant morbidity and mortality in select patient populations, especially pediatrics. Our findings are based on a review study. Studies included are heterogenous with limitations of sample size, human administration, efficacy compared to current treatment standard, and long-term safety data. Further studies are required to assess the efficacy, cost, and safety profile of these and other EAI alternatives.

Article Highlights

- The first review, to our knowledge, that discusses an alternative to the traditionally used epinephrine auto injector

- Synthesizes preliminary data on sublingual and intranasal epinephrine administration
- Examines the need for new drug administration methods in certain situations and populations
- Discusses many drawbacks of the currently used epinephrine auto injector and how novel administration techniques may improve patient care
- Identifies gaps in current literature and suggests possible studies needed to support alternative epinephrine administration

Methods

A thorough literature review of PubMed was conducted for eligible manuscripts using the keywords (epinephrine) AND (replacement) OR (alternative). Additional searches using the same criteria were performed at the same time in the Google Scholar and Mendeley databases. The final analysis included articles written in English. The search was conducted in September and October of 2022, and 32 articles were found to be relevant. Articles were independently screened and assessed by four authors with any disagreements resolved by the decision of an independent reviewer.

Abbreviations

EAI: Epinephrine auto injector

ATP: Adenosine triphosphate

RDST: Rapidly dissolving sublingual tablet

IN: Intranasal

IM: Intramuscular

IV: Intravenous

Declarations

Ethical Approval and Consent to participate

Not applicable

Consent for publication

Given by all authors

Availability of supporting data

Not applicable

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Authors' contributions

Justin M. Ketchem - Study design, manuscript writing, and editing
Elizabeth J. Ketchem - Manuscript writing and figure design
Samarth Mishra - Manuscript writing and literature search
Rohan Kapuria - Manuscript writing and literature search
Ban Majeed - Study design and editing
David W. Walsh - Study design and editing
K.M. Islam - Study design and editing

Conflict of Interest

The authors declare no conflicts of interest.

Disclosures

None

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