ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Epinephrine nasal spray in the treatment of severe type I hypersensitivity reactions

Spray nasal de adrenalina no tratamento de reações alérgicas de tipo I graves

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ABSTRACT

Anaphylaxis is the most severe clinical manifestation of systemic allergic reactions and carries a potential risk of death. Most episodes of anaphylaxis occur outside the hospital setting and, to ensure immediate treatment, alternative epinephrine devices, such as epinephrine autoinjectors, have been developed. However, these devices are not widely available across the world, and there is reluctance to use them, especially among children, who are often needle-phobic. In this context, the development of an epinephrine nasal spray (ENS) represents an interesting alternative for the treatment of anaphylaxis, with favorable results. This study provides a narrative review of ENS in the management of anaphylaxis, addressing its pharmacokinetics, pharmacodynamics, and adverse events across different age groups. Comparative studies between intramuscular and intranasal administration have demonstrated comparable results, supporting the use of ENS as an alternative for the treatment of severe type I hypersensitivity reactions, especially anaphylaxis.

Keywords: Epinephrine, anaphylaxis, adolescent, children, adult.

RESUMO

Anafilaxia é a manifestação clínica mais grave das reações alérgicas sistêmicas e apresenta um risco potencial de morte. A maioria dos episódios de anafilaxia ocorre fora de ambiente hospitalar, e para que haja tratamento imediato, dispositivos alternativos de administração de adrenalina, como os autoinjetores de adrenalina, foram desenvolvidos. Todavia, estes não são disponíveis em boa parte do mundo e há relutância com o seu uso, sobretudo por crianças, geralmente fóbicas por agulha. Assim o desenvolvimento de um *spray* nasal de adrenalina (SNA) representa alternativa interessante no tratamento das anafilaxias, com bons resultados. O presente estudo tem por objetivo realizar revisão narrativa sobre o SNA no tratamento da anafilaxia com relação à sua farmacocinética e farmacodinâmica, assim como os eventos adversos nas diferentes faixas etárias. Estudos comparativos entre a administração de adrenalina intramuscular e por SNA demonstram resultados comparáveis e reforçam a sua utilização como mais uma alternativa para o tratamento de reações alérgicas graves de tipo I, especialmente a anafilaxia.

Descritores: Epinefrina, anafilaxia, adolescente, criança, adulto.

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Submitted Jun 30 2025, accepted Jul 04 2025.

Arq Asma Alerg Imunol. 2025;9(2):227-34.

http://dx.doi.org/10.5935/2526-5393.20250014-en

Introduction

Anaphylaxis is the most severe clinical manifestation of systemic allergic reactions and carries a potential risk of death. International guidelines for the management of anaphylaxis recommend intramuscular (IM) administration of epinephrine (adrenaline) as the first-line treatment, with a well-established safety profile.[1-7]

Despite this, some researchers have recommended alternative routes of administration, many of which contradict current guidelines (Table 1). Epinephrine autoinjectors (EAIs) are an effective, safe, and efficient alternative for treating anaphylaxis, replacing the traditional epinephrine ampule.[1-7]

However, EAIs have significant limitations that may hinder the adequate use of IM epinephrine during anaphylaxis. As a result, innovations involving alternative administration routes may improve treatment use rates and effectiveness. These new devices, which deliver epinephrine via intranasal, sublingual, or transcutaneous routes, are currently in different stages of development and investigation.[8]

In this study, we present a narrative review of the pharmacokinetic (PK), pharmacodynamic (PD), and safety profiles of epinephrine delivered via an epinephrine nasal spray (ENS) in patients experiencing severe type I hypersensitivity reactions, including anaphylaxis. For ethical reasons, double-blind, placebo-controlled studies are not feasible in the treatment of anaphylaxis. Therefore, we reviewed studies published in English, French, Spanish, and German over the past 15 years that evaluated ENS in comparison with injectable products (IM ampules, EAIs). The search terms used were “neffy” OR “epinephrine” OR “anaphylaxis” OR “adrenaline” AND “children” OR “adults.”

EAIs are typically prescribed to individuals at ongoing risk of anaphylaxis in community settings. However, an online survey assessing anaphylaxis management across 66 countries reported that only 60% had access to EAIs, primarily high-income nations.[5] Many countries in South America, Africa/Middle East, and the Asia-Pacific region do not have EAIs available or depend on individual importation. Even in countries where EAIs are commercially available, national policies supporting their availability in public settings are limited, with only 16% of countries permitting such access.[9] Furthermore, because of differences in device design, EAIs are not interchangeable.[10]

Epinephrine is also available as a prefilled syringe (Symjepi), which is FDA-approved but not available in Brazil (Table 1). This option requires individuals

Table 1
Examples of epinephrine delivery devices

Product	Form	Children (15-30 kg)	Adults (>30 kg)
EpiPen	Autoinjector	0.15 mg IM or SC	0.3 mg IM or SC
Amneal*	Autoinjector	0.15 mg IM or SC	0.3 mg IM or SC
AUVI-Q	Autoinjector	0.15 mg IM or SC	0.3 mg IM or SC
Symjepi	Prefilled syringe	0.15 mg IM or SC	0.3 mg IM or SC
Neffy	Nasal spray	1 mg/nostril	2 mg/nostril

IM: intramuscular; SC: subcutaneous.
*Generic product.
Adapted from The Medical Letter on Drugs and Therapeutics.[10,12]

to manually insert the needle and press the plunger, which may be challenging for some, particularly children.[11]

Recently, both the European Medicines Agency (EMA) and the U.S. FDA approved an ENS (*neffy*) as the first noninjectable epinephrine option for the emergency treatment of type I hypersensitivity reactions, including anaphylaxis, in patients aged ≥ 4 years weighing more than 15 kg.[10,12,13]

To whom should preventive epinephrine be prescribed?

Despite significant advances in the management of allergic diseases, important questions remain, as, for obvious ethical reasons, no randomized clinical trials have evaluated the treatment of acute allergic reactions with epinephrine.[14]

Nevertheless, reasonable evidence from observational studies supports the use of epinephrine in the treatment of anaphylaxis. Moreover, large cohort studies indicate that in at least 80% of anaphylaxis episodes, the allergic reaction resolves despite no treatment with epinephrine.[15,16]

According to anaphylaxis guidelines, epinephrine should be prescribed for emergency treatment of a severe exacerbation by the patient/caregiver (particularly via EAI) to any patient with a history of anaphylaxis who cannot easily avoid re-exposure to the causative allergen, especially foods and *Hymenoptera* stings.[1-7,14,17] The guidelines also recommended that EAI be prescribed to patients without prior history of anaphylaxis but with risk factors considered to raise their risk of anaphylaxis, such as a diagnosis of asthma or a prior reaction to trace amounts of allergen.[1-7,14,18]

Although EAIs are commonly prescribed for the immediate treatment of anaphylaxis, fewer than half of patients at risk for severe allergic reactions (including anaphylaxis) carry the products with them, and those who do often delay use during a severe type I hypersensitivity reaction.[19] This delay, often due to needle phobia, can lead to ineffective or late treatment and is associated with significantly increased risks of biphasic reactions, hospitalization, and death.[20-23]

Low utilization rates, especially in the setting of serious adverse outcomes associated with unsuccessful or delayed treatment, represent a significant unmet medical need among patients at risk for severe allergic reactions, including anaphylaxis.[19]

Epinephrine nasal spray

Most severe type I hypersensitivity reactions occur in out-of-hospital settings, and the immediate administration of epinephrine is the only universally recommended first-line treatment.[1-7,19] Needle-free epinephrine delivery options are particularly beneficial for children, among whom needle phobia is especially common. Several medications, including midazolam, diazepam, fentanyl, naloxone, ketamine, and dexmedetomidine, among others, are routinely administered intranasally for a variety of indications.[24]

The ENS consists of 3 key components: (1) epinephrine, the active ingredient; (2) Intravail (dodecylmaltoside), a proprietary absorption-enhancing agent developed to increase the bioavailability of intranasally delivered medications; and (3) a Unit Dose Spray (UDS) device designed to generate an optimal spray pattern and droplet size that maximizes medication delivery to the nasal turbinates.[24]

Epinephrine

Epinephrine is a nonselective agonist of both α- and β-adrenergic receptors, which are all G-protein-coupled. It acts through direct agonism at α- and β-adrenergic receptors, resulting in adenylyl cyclase activation and increased intracellular cyclic adenosine monophosphate production.[25] It stabilizes mast cells by preventing their degranulation and the rapid release of allergic mediators, and directly counteracts nearly all immune mediators of anaphylaxis at end-organs. While anaphylaxis leads to loss of intravascular fluid volume and hypotension, activation of α-adrenergic receptors reduces vasodilation and increases vascular permeability. β-Adrenergic receptors relax bronchial smooth muscle, helping to relieve bronchospasm, wheezing, and dyspnea that may occur during anaphylaxis. Heart rate (HR) and contractility increase via β-adrenergic receptors to maintain blood pressure (BP). In addition, epinephrine can help relax the smooth muscle of the stomach, intestines, uterus, and urinary bladder; improve symptoms such as pruritus, urticaria, and angioedema; and relieve gastrointestinal and genitourinary symptoms associated with anaphylaxis.[25,26]

Intravail

Intravail is a safe alkylsaccharide that alters mucosal viscosity and membrane fluidity to loosen cell-cell junctions, facilitating mucosal absorption.[27] It is soluble in both water and oil and does not cause mucosal irritation or damage.[28]

The combination of epinephrine with Intravail allows greater pharmacologic efficiency while using the lowest effective dose. There are some concerns that the potential vasoconstrictive effect of epinephrine could impair its absorption via nasal spray, but this effect was not observed.[24]

Increased vascular permeability during an allergic reaction could increase epinephrine absorption and increase the risk of overdose. The inclusion of Intravail in the ENS formulation prevents this by enhancing efficacy at lower doses, thereby minimizing the risk of overdose. These factors also contribute to reducing adverse reactions.[24]

Device

Epinephrine is delivered via a UDS device similar to those used in other widely adopted pharmaceutical products. It is easy to use, reliable, and has a very low failure rate (<1 in 100,000 uses). The device delivers 80% of the medication in droplets measuring between 20 and 120 µm, almost all of which are captured on the nasal turbinates.[20]

Pharmacokinetic and pharmacodynamic clinical studies

To date, the conduct of randomized clinical trials to evaluate the efficacy of epinephrine products for the treatment of severe type I hypersensitivity reactions (including anaphylaxis) is considered unethical and impractical; therefore, no such trials have been conducted.[24] Therefore, approval of the ENS was based on multiple clinical trials comparing its PK (mean maximum plasma concentration [C_{max}], time to C_{max} [T_{max}], maximum effect [E_{max}], and time to E_{max} [TE_{max}]) and PD (BP, systolic BP [SBP], diastolic BP [DBP], and HR) with those of approved injectable products. These studies demonstrated that the ENS has a PK profile that is comparable to or better than that of injectable products.[29-32]

An integrated analysis was performed including 4 randomized, crossover trials comparing the PK and PD profiles of manual epinephrine IM injection (0.3 mg), 2 EAIs (EpiPen and Symjepi, both 0.3 mg), and ENS (1 mg) in healthy individuals and individuals with a history of type I allergies (not active) aged 19 to 55 years.[33] It showed that although the ENS resulted in a C_{max} (258 pg/mL) that was lower than but comparable to IM injection (254 pg/mL), Symjepi (438 pg/mL), and EpiPen (503 pg/mL), it led to comparable increases in SBP (E_{max}, 16.9, 10.9, 14.9, and 18.1 mm Hg, respectively). The effect of the ENS on DBP was also markedly more pronounced than that of other products (E_{max}, 9.32, 5.51, 5.78, and 5.93 mm Hg, respectively). According to the authors, the PD profile of the ENS is comparable to that of EpiPen and superior to that of IM injection.[33]

Conversely, Casale et al. conducted a similar study in healthy individuals in which the ENS dose was increased to 2 mg, followed by a repeat dose 10 minutes later. The highest mean epinephrine C_{max} was observed after EpiPen administration (753 pg/mL), and this level remained elevated for 20 minutes, followed by ENS (481 pg/mL) and IM injection (339 pg/mL). [29]

All treatment regimens resulted in an increase from baseline SBP, with the greatest increase occurring after ENS. EpiPen was associated with a faster but less pronounced SBP increase compared with ENS. For all treatments, SBP returned to baseline values within 120 minutes. Mean SBP increase was greater following ENS than IM injection, but not significantly different from EpiPen. Following repeated doses, change from baseline SBP was also greater for ENS compared with EpiPen.[29,30]

Anatomical or structural nasal abnormalities may interfere with the absorption of epinephrine administered via nasal spray. A similar effect might be expected in patients with rhinitis. However, Oppenheimer et al. compared the PD and PK profiles of epinephrine delivered via IM injection and nasal spray in individuals with seasonal allergic rhinitis (SAR), both before and after a nasal allergen challenge. The PD and PK profiles of the ENS were comparable to or better than IM injection, regardless of whether one or two doses were administered, and consistent with findings previously reported in individuals without SAR.[31]

In children and adolescents, PK/PD studies have been conducted with reference to adult data, while reinforcing the presence of age-related differences in these parameters. As children grow, well-recognized physiological increases in BP and HR occur, and

these age-dependent changes must be considered when interpreting PK/PD responses.[25,32,33]

Fleisher et al. conducted a phase 1, multicenter, single-dose PK/PD study of 42 pediatric patients (aged 4-18 years) who were dosed with 1 mg (for body weight 15-30 kg) or 2 mg (for body weight > 30 kg) of ENS. The results were compared with those from 42 healthy adults (aged 22-54 years) who received a single 2-mg dose.[28]

Among pediatric participants who received 1 mg, the mean C_{max} was slightly lower than that of those who received 2 mg (651 vs. 690 pg/mL), and both values were higher than those observed in adults (481 pg/mL).

Both ENS doses resulted in an overall mean increase from baseline SBP; however, transient decreases in DBP were also observed, occurring at 5 minutes for the 1 mg dose and at 10 minutes for the 2 mg dose. No differences were observed between the 2 pediatric doses in terms of HR elevation or mean SBP and DBP values. Adults experienced significantly greater increases in SBP than children, while DBP differences were minimal. HR changes were similar between both children and adults.[28] These increases occur due to activation of adrenergic receptors, which is the main mechanism of action through which epinephrine reverses severe allergic reactions and anaphylaxis.[33] Interestingly, despite the higher epinephrine C_{max} observed in children and adolescents, the maximal increase in mean SBP was significantly lower than that seen in adults. Could this difference be the result of age-related physiological variations?[28] Unlike adults, children demonstrated an initial decrease from baseline DBP with both ENS doses (1 mg and 2 mg), in an age-dependent pattern.[28] This decrease is presumed to result from activation of high-affinity β2-adrenergic receptors, resulting in transient vasodilation. β2-mediated vasodilation subsequently reduces venous return, followed by a decrease in cardiac output, which can potentially lower both SBP and DBP.[29,33] Redistribution of blood flow continues until epinephrine levels rise sufficiently to activate lower-affinity α-adrenergic receptors, resulting in a plasma concentration-dependent shift from vasodilation to vasoconstriction.[34-37]

The relatively high vascular elasticity in children likely makes them more sensitive to this transient β2-mediated vasodilation and the associated transitory decrease in DBP. This effect tends to be more pronounced and to occur earlier with higher ENS doses, and it may also be reflected in SBP changes.[34,36]

Regarding changes in HR, although children showed higher epinephrine concentrations, their HR responses were comparable to those observed in adults. These physiological differences are also likely age-related. Two mechanisms help explain this: (a) a decrease in chronotropic responses to β1-adrenergic stimulation with age, with downregulation and reduced agonist binding of β1-receptors,[35] resulting in a less pronounced HR response in older adults; and (b) reduced baroreflex sensitivity with age,[35] leading to decreased HR modulation (less decrease in HR) in response to rapid increases in BP. Together, the reduced response to β1-adrenergic stimulation and the decreased HR regulation due to a less sensitive baroreflex may minimize differences in cardiac responses to epinephrine in older individuals,[37] resulting in HR responses similar to those observed in pediatric patients, whose HR was reduced by a more sensitive baroreflex with higher epinephrine concentrations.

Hypotension is frequently associated with severe allergic reactions. Therefore, it is important to evaluate how this condition might affect the absorption of intranasally administered epinephrine.[38] A study in anesthetized beagle dogs, assessed under both normal conditions and hypotension associated with anaphylaxis, investigated this question. After being dosed with 1 mg of ENS, the dogs demonstrated significantly higher mean C_{max} of epinephrine during anaphylaxis than under normal conditions (2670 ± 2150 pg/mL vs. 1330 ± 739 pg/mL, $p < 0.05$). The same occurred with the area under the curve (0 to 45 minutes). These findings demonstrate that epinephrine absorption was not impaired by anaphylaxis-associated hypotension.[38]

Overall, when administered to children and adolescents, the ENS demonstrated absorption comparable to or greater than that observed in adults, with increases in SBP and HR consistent with activation of relevant adrenergic receptors at pediatric doses. Regarding DBP, differences in patient responses are largely attributable to normal age-related physiological differences rather than to epinephrine's pharmacologic effect. When compared with data from more than 700 adults, pediatric doses of the ENS performed as expected.[28]

Safety

Epinephrine is the first-line treatment for anaphylaxis and is associated with a well-established safety profile. Effective resolution of anaphylaxis symptoms depends largely on its immediate administration by the patient/caregiver. However, the potential for overdose and serious cardiac adverse effects exists with any route of administration, although this risk is lower with IM injection compared with intravenous administration.[39]

Epinephrine should be administered with caution in pregnant women, older adults, and patients with underlying heart disease or those taking cardiac glycosides, diuretics, or antiarrhythmics, as it may worsen angina or precipitate ventricular arrhythmias (including fatal ventricular fibrillation). Individuals taking antidepressants or those with thyroid disorders, diabetes, or hypertension may be at increased risk for adverse reactions. Epinephrine may temporarily exacerbate underlying conditions and/or worsen symptoms in patients with hyperthyroidism, Parkinson's disease, diabetes, and renal insufficiency.[6,8]

Although the ENS contains metabisulfite in its formulation, this should not preclude its use in patients with sulfite sensitivity.[6,8] Mucosal changes may persist for up to 2 weeks following ENS use and may potentially increase the systemic absorption of medications applied intranasally, including epinephrine itself.[6,8]

The ENS is supplied as a single-dose (1 mg or 2 mg) spray to be administered as follows: 1 mg for children aged ≥ 4 years weighing 15-30 kg; and 2 mg for patients weighing ≥ 30 kg.[6,8] The recommended regimen is one spray administered into one nostril. If symptoms do not improve after 5 minutes, a second dose may be applied to the same nostril using a new nasal spray.[6,8]

Correct use of the device is essential, even by untrained individuals relying solely on written instructions. Hernandez-Trujillo et al. conducted a human factor study of ENS in adults, juveniles, caregivers, and patients. All participants were able to carry the case containing 2 devices, open it during a simulated allergic emergency, and successfully administer the product both once and twice (10 minutes apart) in the same nostril.[9]

Adverse events occur in approximately 7%-19% of cases and are generally mild. Common reactions include nasal discomfort, headache, rhinorrhea, dizziness, nausea, vomiting, throat irritation or dryness, paresthesia, sneezing, upper airway congestion, epistaxis, nasal dryness, fatigue, and nervousness.[6,8]

Fleischer et al. reported adverse events in 52.4% of patients who received ENS 1 mg and 66.7% of those who received 2 mg. In the 1 mg group, the most common events were nasal congestion (19%), upper respiratory tract congestion (14.3%), dry throat, nasal dryness, and paresthesia (9.5%). In the 2 mg group, the most common were nasal discomfort, rhinorrhea, and intranasal paresthesia (19%), sneezing (14.3%), rhinalgia, epistaxis, paresthesia, fatigue, and feeling jittery (9.5%). No gastrointestinal adverse events (nausea or vomiting) were reported. Most events were mild and resolved quickly. No serious adverse reactions or study withdrawals occurred.[28]

According to the manufacturer, the ENS should be stored at room temperature, with excursions permitted up to 50 °C. At temperatures below –15 °C, the solution freezes and the device fails to release epinephrine. The shelf-life of the ENS (*neffy*) is 30 months, longer than that of injectable products, which typically have a shelf-life of 12 to 18 months.[6,8]

Conclusion

To date, PK and PD studies of ENS have demonstrated clinical efficacy comparable to IM epinephrine (ampule or EAI) in both adults and children.[31,40] The ENS represents an innovative and promising alternative, particularly for patients who face barriers to using injectable devices.

References

1. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010;126:S1-S58.
2. Ewan P, Brathwaite N, Leech S, Luyt D, Powell R, Till S, et al. BSACI guideline: prescribing an adrenaline auto-injector. Clin Exp Allergy. 2016;46:1258-80.
3. Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Fernandez Rivas M, Fineman S, et al. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J. 2020;13(10):100472.
4. Muraro A, Worm M, Alviani C, Cardona V, DunnGalvin A, Garvey LH, et al. EAACI guidelines: Anaphylaxis (2021 update). Allergy. 2022;77(2):357-77.

5. Australasian Society of Clinical Immunology and Allergy. ASCIA guidelines—adrenaline (epinephrine) injector prescription [Internet]. Available from: https://www.allergy.org.au/hp/anaphylaxis/adrenaline-injector-prescription. Accessed on: Jun 25 2025.
6. Golden DBK, Wang J, Waserman S, Shaker MS, Stukus DR, Wang J, et al. Anaphylaxis: A 2023 practice parameter update. Ann Asthma Allergy Immunol. 2024;132(2):124-76.
7. Wang J, Lieberman JA, Wallace DV, Waserman S, Golden DBK. Anaphylaxis in Practice: A Guide to the 2023 Practice Parameter Update. J Allergy Clin Immunol Pract. 2024;12(9):2325-36.
8. Pouessel G, Neukirch C. Alternatives to Injectable Adrenaline for Treating Anaphylaxis. Clin Exp Allergy. 2024;55(1):36-51.
9. Tanno LK, Worm M, Ebisawa M, Ansotegui IL, Senna G, Fineman S, et al. Global disparities in availability of epinephrine auto-injectors. World Allergy Organ J. 2023;16(10):100821.
10. The Medical Letter on Drugs and Therapeutics. An Epinephrine Nasal Spray (neffy) for Anaphylaxis. Med Lett Drugs Ther. 2024 Oct 14;66(1713):163-4.
11. The Medical Letter on Drugs and Therapeutics. An epinephrine prefilled syringe (Symjepi) for anaphylaxis. Med Lett Drugs Ther. 2019;61:25.
12. The Medical Letter on Drugs and Therapeutics. In Brief: Epinephrine 1 mg Nasal Spray (neffy). Med Lett Drugs Ther. 2025;67(1727):71.
13. Hernandez-Trujillo V, Brooks J, Tachdjian R, Dorsey BT, Lowenthal R, Tanimoto S. Successful Administration of neffy, Epinephrine Nasal Spray, When Provided with a Two-Dose Carrying Case – A Human Factor Study. In: Annual Meeting of the American College of Allergy, Asthma and Immunology; October 24-28, 2024; Boston, MA. Available from: https://ir.ars-pharma.com/static-files/e890cf91-c87a-4b76-9472-181186c4c18f. Accessed on: Jun 25 2025.
14. Dribin TE, Waserman S, Turner PJ. Who Needs Epinephrine? Anaphylaxis, Autoinjectors, and Parachutes. J Allergy Clin Immunol Pract. 2023;11(4):1036-46.
15. Noimark L, Wales J, Du Toit G, Pastacaldi C, Haddad D, Gardner J, et al. The use of adrenaline autoinjectors by children and teenagers. Clin Exp Allergy. 2012;42:284-92.
16. Grabenhenrich LB, Dölle S, Ruëff F, Renaudin JM, Scherer K, Pföhler C, et al. Epinephrine in severe allergic reactions: the European Anaphylaxis Register. J Allergy Clin Immunol Pract. 2018;6:1898-1906.e1
17. Kemp AS. EpiPen epidemic: suggestions for rational prescribing in childhood food allergy. J Paediatr Child Health. 2003;39:372-5.
18. Shaker MS, Wallace DV, Golden DBK, Oppenheimer J, Bernstein JA, Campbell RL, et al. Anaphylaxis-a 2020 practice parameter, and grading of recommendations, assessment, development and evaluation (GRADE) analysis. J Allergy Clin Immunol. 2020;145:1082-123.
19. Ellis AK, Casale TB, Kaliner M, Oppenheimer J, Spergel JM, Fleischer DM, et al. Development of neffy, an Epinephrine Nasal Spray, for Severe Allergic Reactions. Pharmaceutics. 2024;16(6):811.
20. Fleming JT, Clark S, Camargo CA, Rudders SA. Early treatment of food-induced anaphylaxis with epinephrine is associated with a lower risk of hospitalization. J Allergy Clin Immunol Pract. 2015;3:57-62.
21. Patel N, Chong KW, Yip AYG, Ierodiakonou D, Bartra J, Boyle RJ, et al. Use of multiple epinephrine doses in anaphylaxis: A systematic review and meta-analysis. J Allergy Clin Immunol. 2021;148:1307-15.
22. Liu X, Lee S, Lohse CM, Hardy CT, Campbell RL. Biphasic reactions in emergency department anaphylaxis patients: A prospective cohort study. J Allergy Clin Immunol Pract. 2020;8:1230-8.
23. Turner PJ, Jerschow E, Umasunthar T, Lin R, Campbell DE, Boyle RJ. Fatal anaphylaxis: Mortality rate and risk factors. J Allergy Clin Immunol Pract. 2017;5:1169-78.
24. Ring J, Klimek L, Worm M. Adrenaline in the acute treatment of anaphylaxis. Medicine. 2018;115:528-34.
25. Brown JC, Simons E, Rudders SA. Epinephrine in the management of anaphylaxis. J. Allergy Clin Immunol Pract. 2020;8:1186-95.
26. Hogan RE, Gidal BE, Koplowitz B, Koplowitz LP, Lowenthal RE, Carrazana E. Bioavailability and safety of diazepam intranasal solution compared to oral and rectal diazepam in healthy volunteers. Epilepsia. 2020;61:455-64.
27. Rabinowicz AL, Carrazana E, Maggio ET. Improvement of intranasal drug delivery with Intravail alkylsaccharide excipient as a mucosal absorption enhancer aiding in the treatment of conditions of the central nervous system. Drugs RD. 2021;21:361-9.
28. Fleischer DM, Li HH, Talreja N, Lockey RF, Kaliner MA, Wainford RD, et al. Pharmacokinetics and Pharmacodynamics of neffy, Epinephrine Nasal Spray, in Pediatric Allergy Patients. J Allergy Clin Immunol Pract. 2025;13(6):1335-1341.e1
29. Casale TB, Ellis AK, Nowak-Wegrzyn A, Kaliner M, Lowenthal R, Tanimoto S. Pharmacokinetics/pharmacodynamics of epinephrine after single and repeat administration of neffy, EpiPen, and manual intramuscular injection. J Allergy Clin Immunol. 2023;152:1587-96.
30. Casale TB, Oppenheimer J, Kaliner M, Lieberman JA, Lowenthal R, Tanimoto S. Adult pharmacokinetics of self-administration of epinephrine nasal spray 2.0 mg versus manual intramuscular epinephrine 0.3 mg by health care provider. J Allergy Clin Immunol Pract. 2023;12:500-2.
31. Oppenheimer J, Casale TB, Camargo CA, Fleischer DM, Bernstein D, Lowenthal R, et al. Upper respiratory tract infections have minimal impact on neffy's pharmacokinetics or pharmacodynamics. J Allergy Clin Immunol Pract. 2024;12:1640-3.
32. Tilley DG, Houser SR, Koch WJ. Adrenergic Agonists and Antagonists. In: Brunton LL, Knollmann BC. eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14ª ed. New York: McGraw-Hill Education; 2023. p.947.
33. Tanimoto S, Kaliner M, Lockey RF, Ebisawa M, Koplowitz LP, Koplowitz B, et al. Pharmacokinetic and pharmacodynamic comparison of epinephrine, administered intranasally and intramuscularly: An integrated analysis. Ann Allergy Asthma Immunol. 2023;130(4):508-514.e1.
34. Worm M, Nguyen DT, Rackley R, Muraro A, DuToit G, Lawrence T, et al. Epinephrine delivery via epipen, auto-injector or manual syringe across participants with a wide range of skin-to-muscle distances. Clin Transl Allergy. 2020;10:1-13.
35. White M, Leenen FHH. Aging and cardiovascular responsiveness to beta-agonist in humans: role of changes in beta-receptor responses versus baroreflex activity. Clin Pharmacol Ther. 1996;56:543-53.
36. Monahan KD. Effect of aging on baroreflex function in humans. Am J Physiol Regul Integr Comp Physiol. 2007;293:R3-R12.
37. Leenen FH, Coletta E, Fourney A, WhiteR. Aging and cardiac responses to epinephrine in humans: role of neuronal uptake. Am J Physiol Heart Circ Physiol. 2005;288:H2498-H2503.
38. Sparapani S, Authier S, Lowenthal R, Tanimoto S. The impact of anaphylaxis on the absorption of intranasal epinephrine in anaesthetized non-naive beagle dogs. J Allergy Clin Immunol Glob. 2023;2(4):100165.
39. Pauw EK, Stubblefield WB, Wrenn JO, Brown SK, Cosse MS, Curry ZS, et al. Frequency of cardiotoxicity following intramuscular administration of epinephrine in emergency department patients with anaphylaxis. J Am Coll Emerg Physicians Open. 2024;5:e13095.

40. Oppenheimer J, Casale T, Spergel J, Bernstein D, Camargo Jr CA, Ellis AK, et al. Pharmacokinetics and Pharmacodynamics Following Repeat Dosing of neffy, Epinephrine Nasal Spray, Versus Intramuscular Injection During Induced Allergic Rhinitis. In: Annual Meeting of the American College of Allergy, Asthma and Immunology; October 24-28, 2024; Boston, MA. Available from: https://ir.ars-pharma.com/static-files/1deda89c-2ed2-4512-a927-83182e1c330b. Accessed on: Jun 29 2025.

No conflicts of interest declared concerning the publication of this article.

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