# Intranasal epinephrine: Does it stack up to the intramuscular standard?

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Anaphylaxis demands rapid epinephrine administration, a fact clinicians know well. But the reliance on intramuscular (IM) injection presents practical barriers for patients and caregivers, leading to underuse and delayed treatment. A needle-free alternative has long been sought to address these adherence challenges, particularly for those with a known allergy history.

neffy (epinephrine nasal spray) offers a novel approach, but its pharmacokinetic profile, especially in the context of nasal obstruction from allergic rhinitis, required rigorous evaluation. The Pharmacokinetics and Pharmacodynamics Following Repeat Dosing of neffy (Epinephrine Nasal Spray) Versus Intramuscular Injection During Induced Allergic Rhinitis study, published in J Allergy Clin Immunol Pract, directly compared intranasal and intramuscular epinephrine in a challenging clinical scenario.1

**KEY TAKEAWAYS**

- The Pivot: Intranasal epinephrine (neffy) demonstrated a pharmacokinetic profile comparable to intramuscular epinephrine, even in the presence of induced allergic rhinitis.
- The Data: The geometric mean ratio for AUC0-30min (neffy/IM) was 0.84 (90% CI, 0.76-0.93), indicating similar early systemic exposure.
- The Action: Clinicians can consider intranasal epinephrine as a viable, needle-free option for severe allergic reactions, potentially improving adherence and reducing treatment delays.

Anaphylaxis remains a life-threatening emergency, with epinephrine being the cornerstone of treatment. Despite its vital role, adherence to carrying and using epinephrine autoinjectors is suboptimal. Patients often cite needle phobia, inconvenience, and fear of improper administration as reasons for not carrying their prescribed devices, a persistent problem that our previous coverage has explored. This leads to delayed or missed doses, increasing the risk of severe outcomes. A non-injectable, rapidly absorbed formulation could significantly improve patient compliance and, by extension, clinical outcomes.1

Oppenheimer and colleagues designed a randomized, open-label, two-period crossover study to assess the pharmacokinetics (PK) and pharmacodynamics (PD) of neffy compared with intramuscular epinephrine. The trial enrolled 36 healthy adults with a history of seasonal allergic rhinitis. Investigators induced allergic rhinitis with nasal obstruction using a validated environmental exposure chamber, creating a real-world challenge for intranasal drug delivery. Participants received either a single dose of neffy (2 mg) or IM epinephrine (0.3 mg) in a crossover design, with

a washout period between treatments. The primary PK endpoints included maximum plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) at various intervals.1

## The Pharmacokinetic Profile in Induced Rhinitis

The study found that neffy achieved systemic epinephrine exposure comparable to IM epinephrine, even under conditions of induced allergic rhinitis. The geometric mean ratio for AUC0-30min (neffy/IM) was 0.84 (90% CI, 0.76-0.93), falling within the predefined equivalence range of 0.80-1.25. This early exposure is critical for anaphylaxis treatment, where rapid onset of action is paramount. Cmax for neffy was 1008 pg/mL (90% CI, 896-1133 pg/mL) compared to 1200 pg/mL (90% CI, 1067-1350 pg/mL) for IM epinephrine, with a geometric mean ratio of 0.84 (90% CI, 0.73-0.97). While Cmax was slightly lower for neffy, the rapid absorption kinetics suggest clinical relevance.1

Peak plasma concentrations (Tmax) were also similar, with a median Tmax of 15 minutes for neffy and 10 minutes for IM epinephrine. This difference of 5 minutes is unlikely to be clinically meaningful in the acute management of anaphylaxis, where the goal is to achieve therapeutic levels quickly. The study also evaluated repeat dosing, administering a second dose 10 minutes after the first. This simulated a scenario where a patient might require additional epinephrine due to persistent or worsening symptoms. The PK profile remained consistent with the first dose, indicating reliable absorption even with repeated intranasal administration.1

The investigators also assessed pharmacodynamic markers, including changes in blood pressure and heart rate. Both neffy and IM epinephrine produced similar increases in systolic blood pressure (SBP) and heart rate (HR), reflecting comparable systemic adrenergic effects. The mean maximum increase in SBP was 21.2 mmHg for neffy and 24.7 mmHg for IM epinephrine. For heart rate, the mean maximum increase was 16.2 bpm for neffy and 18.9 bpm for IM epinephrine. These PD responses confirm that the intranasal formulation delivers a biologically active dose of epinephrine, triggering the expected physiological responses necessary to counteract anaphylaxis.1

## Safety and Tolerability

neffy was generally well-tolerated in the study population. The most common adverse events (AEs) associated with neffy were mild and transient, primarily related to nasal irritation. These included nasal discomfort, sneezing, and rhinorrhea. No serious adverse events were reported with either treatment. The safety profile is an important consideration for a product intended for self-administration, as a favorable tolerability profile can enhance patient acceptance and adherence. The local nasal effects were consistent with other intranasal medications and did not appear to significantly impede absorption.1

The study specifically addressed the concern that allergic rhinitis with nasal obstruction might impair intranasal drug absorption. By inducing allergic rhinitis in participants, the researchers created a challenging environment for nasal drug delivery. The consistent PK and PD results under these conditions suggest that neffy's absorption is robust enough to be effective even when patients experience nasal congestion, a common symptom during allergic reactions. This is a vital point, as many patients experiencing anaphylaxis may also have underlying allergic rhinitis or develop nasal symptoms as part of their allergic reaction.1

## The Mechanism of Intranasal Delivery

Intranasal drug delivery bypasses first-pass metabolism, allowing for rapid absorption directly into the systemic circulation through the highly vascularized nasal mucosa. This route offers a non-invasive alternative to injections, which

can be particularly advantageous in emergency situations or for individuals with needle phobia. The formulation of neffy is designed to optimize absorption, ensuring that epinephrine can quickly reach therapeutic concentrations. The nasal cavity provides a large surface area for absorption, and the rich blood supply facilitates rapid drug uptake.1

The challenge with intranasal delivery, particularly for a drug like epinephrine that requires precise dosing and rapid onset, lies in ensuring consistent absorption. Factors such as nasal congestion, mucociliary clearance, and individual anatomical variations can influence drug uptake. The study's design, which included induced allergic rhinitis, aimed to simulate a worst-case scenario for absorption, providing stronger evidence for the drug's reliability. The positive results suggest that the formulation effectively overcomes these potential barriers.1

## Comparing Intranasal to Intramuscular

Intramuscular epinephrine has been the standard of care for anaphylaxis for decades due to its rapid and reliable absorption. But its administration requires a needle, which can be a significant barrier for many. Patients may hesitate to use an autoinjector, or caregivers may be reluctant to administer it, leading to delays that can be life-threatening. The challenges of precise dosing and administration are well-documented across various drug classes. neffy offers a needle-free alternative that could address these issues, potentially increasing the likelihood of timely administration.1

The comparable PK and PD profiles observed in this study are important for patient safety and efficacy. While Cmax was slightly lower with neffy, the rapid achievement of therapeutic concentrations and similar AUC0-30min values indicate that the intranasal route can provide sufficient systemic exposure to manage an acute anaphylactic reaction. The early time points for AUC are particularly important, as they reflect the amount of drug available in the bloodstream during the critical initial phase of anaphylaxis. The data suggest that neffy could offer a similar therapeutic window to IM epinephrine, but with the added benefit of a less intimidating administration method.1

## Where it Falls Short

The study was conducted in healthy adults with induced allergic rhinitis, not in patients actively experiencing anaphylaxis. While induced rhinitis provides a relevant challenge for nasal absorption, the physiological state of a patient in full-blown anaphylaxis, with potential hypoperfusion or altered nasal blood flow, might differ. The generalizability of these findings to the full spectrum of anaphylactic reactions, particularly the most severe cases, requires further investigation in real-world settings. The relatively small sample size of 36 participants also means that rare adverse events or subtle PK differences might not have been detected.1

But the open-label design is an obvious caveat. While PK/PD studies are often open-label due to the nature of drug administration and measurement, it introduces potential for bias in subjective assessments, though objective PK/PD markers mitigate this to some extent. The study also focused on a single dose of neffy (2 mg) and IM epinephrine (0.3 mg). While repeat dosing was explored, the optimal dosing strategy for neffy in various anaphylaxis scenarios, particularly in pediatric populations or those with specific comorbidities, still needs to be fully elucidated.1

The trial was not powered to detect differences in clinical outcomes, such as resolution of anaphylaxis symptoms or prevention of biphasic reactions. Its primary objective was to establish pharmacokinetic and pharmacodynamic equivalence. Future studies would need to evaluate neffy in a clinical trial setting with actual anaphylaxis patients to confirm its efficacy in preventing severe outcomes. Still, the robust PK/PD data provide a strong foundation for its potential clinical utility.1

### CLINICAL IMPLICATIONS

The data on intranasal epinephrine are compelling. For years, clinicians have grappled with the reality that many patients, particularly those with needle phobia or anxiety, do not carry or use their autoinjectors as prescribed. This needle-free option could significantly improve adherence, ensuring more patients have immediate access to life-saving epinephrine when an anaphylactic reaction strikes.

Consider the practical implications in a busy general practice. Educating patients on proper autoinjector use is time-consuming, and retention of technique can be poor. A simple nasal spray, akin to a common decongestant, could reduce the psychological barrier to administration, making it more likely that a patient or caregiver will act quickly. This ease of use might also benefit school nurses or other non-medical personnel who may need to administer epinephrine in an emergency.

But the slight difference in Cmax, while within equivalence margins, warrants attention. While the early AUC is comparable, some clinicians may still prefer the established rapid peak of IM epinephrine for the most severe, rapidly progressing cases. The real-world effectiveness in patients with profound shock or compromised nasal perfusion remains an open question that future post-marketing data will need to address.

The introduction of neffy represents a significant step forward in anaphylaxis management. It does not replace IM epinephrine, but rather offers a valuable alternative that could fill a critical gap in patient care, especially for those who struggle with injectable therapies. This could lead to better patient outcomes by simply making epinephrine more accessible and less intimidating.

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### REFERENCES

1. 1. Oppenheimer J, Casale TB, Spergel JM. Pharmacokinetics and Pharmacodynamics Following Repeat Dosing of neffy (Epinephrine Nasal Spray) Versus Intramuscular Injection During Induced Allergic Rhinitis. J Allergy Clin Immunol Pract 2026. https://pubmed.ncbi.nlm.nih.gov/41687867/

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