Intranasal Epinephrine: Is a Needle-Free Option Viable for Anaphylaxis?

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Anaphylaxis demands rapid epinephrine administration, but the prospect of self-injecting a needle can deter patients, leading to delayed or missed doses. A needle-free alternative could address this critical barrier, potentially improving outcomes in a life-threatening emergency. The challenge lies in ensuring adequate and consistent absorption, particularly through a nasal mucosa that may be compromised during an allergic reaction.

KEY TAKEAWAYS

- The Pivot: Intranasal epinephrine (neffy) achieved comparable systemic exposure to intramuscular epinephrine, even in the presence of induced allergic rhinitis.
- The Data: The geometric mean ratio for AUC0- of neffy 2.0 mg vs. IM epinephrine 0.3 mg was 0.86 (90% CI, 0.77-0.96) in patients with allergic rhinitis.
- The Action: Clinicians should consider intranasal epinephrine as a potential needle-free option for patients requiring rapid epinephrine, acknowledging its pharmacokinetic profile is robust even with nasal congestion.

Severe allergic reactions require immediate intervention with epinephrine, typically delivered via intramuscular (IM) injection. This method ensures rapid systemic absorption, which is vital for counteracting the swift progression of anaphylaxis. But patient reluctance to use an auto-injector, often due to needle phobia or anxiety during an emergency, remains a significant hurdle to timely administration. This reluctance can lead to delayed treatment, increasing morbidity and mortality. The development of a needle-free epinephrine option, such as an intranasal spray, aims to overcome these barriers, offering a more accessible and potentially less intimidating route of administration for patients and caregivers.1 Oppenheimer and colleagues investigated the pharmacokinetic and pharmacodynamic profiles of neffy (epinephrine nasal spray) compared with IM epinephrine injection. The study specifically focused on how repeat dosing of the intranasal formulation performed in the presence of induced allergic rhinitis, a condition that could theoretically impair nasal drug absorption. This was a critical design element, as patients experiencing severe allergic reactions often present with nasal congestion and inflammation, which might alter the drug's uptake. The trial enrolled 120 healthy adults, aged 18 to 55 years, who had a history of seasonal allergic rhinitis. Participants were randomized to receive either neffy 2.0 mg or IM epinephrine 0.3 mg. The study was published in the Journal of Allergy and Clinical Immunology: In Practice.1

Evaluating Pharmacokinetics in Allergic Rhinitis

The study employed a randomized, open-label, two-period, two-treatment, crossover design. Each participant received both neffy and IM epinephrine, separated by a washout period. This crossover design allowed for within-subject

comparisons, minimizing inter-individual variability and strengthening the pharmacokinetic analysis. The primary pharmacokinetic endpoints included area under the curve from time zero to infinity (AUC0-) and maximum plasma concentration (Cmax). Secondary endpoints included time to Cmax (Tmax) and various pharmacodynamic measures, such as changes in heart rate, blood pressure, and nasal blood flow.1

Participants underwent an induced allergic rhinitis challenge before drug administration. This involved intranasal allergen exposure to simulate the physiological changes associated with a natural allergic reaction, including nasal obstruction and increased mucus production. The researchers carefully monitored nasal symptoms and airflow to confirm the presence of rhinitis before each dosing period. This rigorous approach ensured that the study conditions accurately reflected a real-world scenario where a patient might need epinephrine while experiencing significant nasal congestion.1

Neffy 2.0 mg achieved systemic epinephrine exposure comparable to IM epinephrine 0.3 mg, even in the presence of induced allergic rhinitis. The geometric mean ratio for AUC0- of neffy 2.0 mg versus IM epinephrine 0.3 mg was 0.86 (90% CI, 0.77-0.96). This indicates that the total amount of epinephrine absorbed over time was within an acceptable range relative to the IM standard. For Cmax, the geometric mean ratio was 0.67 (90% CI, 0.58-0.77), suggesting that while the peak concentration was lower with the nasal spray, it still provided substantial systemic levels.1

The Tmax for neffy was slightly longer than for IM epinephrine, with median values of 20 minutes versus 10 minutes, respectively. This difference in onset time is a critical consideration for acute anaphylaxis, where every minute counts. But the study also evaluated the time to reach a plasma epinephrine concentration of 100 pg/mL, a threshold often associated with a therapeutic effect. Neffy achieved this threshold within a clinically relevant timeframe, suggesting its potential utility despite the slightly delayed Tmax.1

Pharmacodynamic Responses and Safety Profile

Pharmacodynamic assessments supported the pharmacokinetic findings. Both neffy and IM epinephrine produced dose-dependent increases in heart rate and systolic blood pressure, consistent with the known physiological effects of epinephrine. The magnitude and duration of these changes were generally comparable between the two routes of administration, reinforcing the notion that intranasal delivery can elicit a meaningful systemic response. Nasal blood flow, measured by laser Doppler flowmetry, showed a transient decrease following neffy administration, indicating local vasoconstriction, which is a desirable effect for reducing nasal congestion and potentially enhancing absorption.1

The safety profile of neffy was consistent with that of IM epinephrine. The most common adverse events reported were headache, nausea, and palpitations, all of which are well-known effects of epinephrine. Local nasal irritation was also reported with neffy, but these events were generally mild and transient, resolving without intervention. No serious adverse events occurred in either treatment group. The study authors concluded that neffy was well-tolerated, with no unexpected safety signals emerging from repeat dosing in the presence of allergic rhinitis.1

The study's focus on induced allergic rhinitis is a strength, directly addressing a common clinical concern regarding intranasal drug delivery during an allergic episode. The results suggest that even with nasal obstruction, neffy maintains a pharmacokinetic profile that could be clinically effective. This is particularly relevant for patients who might experience nasal symptoms as part of their allergic reaction. The dosing considerations for intranasal therapies are often complex, and this trial provides valuable data on epinephrine's performance in a challenging physiological state.1

But the study was conducted in healthy adults with induced rhinitis, not in patients experiencing actual anaphylaxis. The physiological stress and circulatory changes during true anaphylaxis could potentially alter drug absorption kinetics.

While induced rhinitis mimics some aspects of an allergic reaction, it does not fully replicate the systemic inflammatory response and cardiovascular compromise seen in severe anaphylaxis. This is an important distinction when extrapolating these findings to emergency clinical practice.1

Another limitation is the relatively small sample size of 120 participants. While sufficient for pharmacokinetic comparisons, it may not capture rare adverse events or subtle differences in efficacy across a broader patient population. The study also did not directly compare neffy to IM epinephrine in terms of clinical outcomes in anaphylaxis, such as resolution of symptoms or need for rescue medication. The primary focus was on pharmacokinetic equivalence, which is a necessary first step but not a substitute for outcome data.1

The slightly longer Tmax for neffy compared to IM epinephrine warrants careful consideration. In a rapidly progressing anaphylactic reaction, a 10-minute difference in peak concentration could be clinically significant. While neffy did achieve therapeutic concentrations within a reasonable timeframe, clinicians must weigh this against the immediate onset typically associated with IM administration. This is a common challenge with alternative routes of administration, as seen in discussions around desmopressin dosing refinements for central diabetes insipidus, where precise timing of effect is paramount.1

The open-label design is an obvious caveat. While blinding is challenging for different routes of administration, the lack of blinding could introduce bias, particularly in the reporting of subjective adverse events. But pharmacokinetic endpoints are objective measures, which mitigates some of this concern. The study also did not explore the impact of severe nasal obstruction or other co-morbidities that might affect nasal absorption, such as chronic sinusitis or nasal polyps. These factors could further complicate the real-world effectiveness of intranasal epinephrine.1

Still, the data from Oppenheimer and colleagues provide a compelling argument for the pharmacokinetic viability of intranasal epinephrine. The ability to deliver epinephrine effectively through the nasal route, even with congestion, represents a significant step forward in addressing the unmet need for a needle-free option. This could empower more patients to self-administer epinephrine promptly, potentially reducing the incidence of severe outcomes from anaphylaxis. The Oxford Handbook of Clinical Immunology and Allergy offers further insights into the management of such conditions.1

The next phase of research will need to focus on real-world effectiveness and safety in actual anaphylaxis patients, including those with varying degrees of nasal congestion and systemic compromise. Comparative effectiveness trials against IM epinephrine in emergency settings would provide the definitive evidence needed for widespread clinical adoption. These trials would need to assess critical outcomes such as time to symptom resolution, need for additional epinephrine doses, and rates of hospital admission.1

CLINICAL IMPLICATIONS

The data on intranasal epinephrine are encouraging, particularly the demonstration of comparable systemic exposure even with induced allergic rhinitis. This addresses a major concern for clinicians: whether a nasal spray could deliver enough drug when a patient's nasal passages are already inflamed. The pharmacokinetic profile suggests it can, offering a genuine alternative for patients who fear needles or struggle with auto-injector use.

For general practitioners, this means a potential expansion of options for patients at risk of anaphylaxis. While

> IM epinephrine remains the gold standard, a needle-free device like neffy could improve adherence and reduce treatment delays in the critical moments following an allergic reaction. The slightly longer Tmax compared to IM injection will require careful patient education, emphasizing that prompt administration remains paramount. The industry has long sought a more patient-friendly epinephrine delivery system. This development could significantly impact patient quality of life and reduce anxiety associated with carrying and using an auto-injector. But regulatory bodies will undoubtedly demand robust clinical outcome data in actual anaphylaxis patients before broad recommendations are made.
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> The unanswered question remains whether this pharmacokinetic equivalence translates into equivalent clinical efficacy in the chaotic environment of true anaphylaxis. Future studies must directly compare clinical outcomes, not just drug levels, to solidify the role of intranasal epinephrine in emergency management.

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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. PMID: 41687867.

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