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IMMUNOGENICITY ACROSS ROUTES: NASAL VS. SUBCUTANEOUS DRUG ADMINISTRATION

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ABSTRACT

The route of drug administration plays a critical role in determining immunogenicity, influencing both the intensity and duration of the immune response. This paper examines the differences in immunogenicity between nasal and subcutaneous drug administration, focusing on vaccine delivery, biologics, and therapeutic proteins. While nasal administration offers a non-invasive route that can stimulate both mucosal and systemic immunity, subcutaneous administration elicits robust systemic responses with prolonged drug bioavailability. This review discusses the immunological mechanisms, advantages, limitations, and clinical implications of both administration routes.

I. INTRODUCTION

The route of drug administration plays a pivotal role in determining the pharmacokinetics, efficacy, and immunogenicity of a therapeutic agent. Immunogenicity, which refers to the ability of a substance to provoke an immune response, is a critical factor in drug development, particularly for vaccines, biologics, and protein-based therapeutics. Different routes of administration influence how the immune system recognizes and responds to an antigen, ultimately affecting clinical outcomes. Among the various drug delivery pathways, nasal and subcutaneous administration are commonly employed for their distinct advantages in eliciting immune responses. Nasal drug administration is a non-invasive method that allows direct interaction with the mucosal immune system, making it an attractive route for vaccine delivery and peptide-based therapies. On the other hand, subcutaneous injection involves the administration of drugs into the subcutaneous tissue, leading to a slower but sustained absorption into the systemic circulation, which is beneficial for long-term drug action. Understanding the differences in immunogenicity between these two routes is essential for optimizing therapeutic efficacy and minimizing adverse immune reactions.

Nasal drug administration has garnered significant attention due to its ability to induce both mucosal and systemic immune responses. The nasal mucosa is lined with antigen-presenting cells (APCs) that capture antigens and present them to immune cells, initiating an immune response. The presence of the nasal-associated lymphoid tissue (NALT) enhances immune activation, promoting the production of secretory IgA, which plays a crucial role in mucosal immunity. This makes nasal administration particularly effective for vaccines targeting respiratory pathogens such as influenza, COVID-19, and tuberculosis. Additionally, nasal delivery bypasses first-pass metabolism and enzymatic degradation in the gastrointestinal tract, allowing for improved bioavailability of certain drugs, especially peptides and proteins. However, the effectiveness of nasal administration is often limited by factors such as mucociliary clearance, enzymatic degradation, and variability in drug absorption across individuals. Additionally, ensuring drug stability and optimal formulation remains a challenge, as many biologics degrade rapidly when exposed to the nasal environment.

Subcutaneous administration, in contrast, is widely used for vaccines, insulin therapy, and monoclonal antibody treatments due to its ability to provide sustained and controlled drug

release. Unlike nasal administration, which primarily stimulates mucosal immunity, subcutaneous injection elicits a strong systemic immune response characterized by IgG production. The absorption of drugs from the subcutaneous tissue occurs through diffusion into the lymphatic system and subsequent entry into the bloodstream, leading to prolonged drug availability. This makes subcutaneous administration particularly advantageous for long-term therapies, as it reduces the need for frequent dosing. Moreover, subcutaneous delivery minimizes the enzymatic degradation faced by oral and nasal routes, ensuring higher drug stability. However, the major downside of subcutaneous administration is the potential for injection site reactions, including pain, swelling, and inflammation. Furthermore, it carries a higher risk of unwanted immunogenicity, particularly in the case of therapeutic proteins, where anti-drug antibody (ADA) formation can compromise drug efficacy and safety.

The immune responses triggered by nasal and subcutaneous administration differ significantly due to their interaction with distinct immune pathways. Nasal administration primarily engages the mucosal immune system, leading to the activation of dendritic cells, macrophages, and lymphocytes in the NALT. This results in the production of both IgA and IgG antibodies, which provide protection against infections at mucosal surfaces while also contributing to systemic immunity. In contrast, subcutaneous administration predominantly activates systemic immunity through antigen presentation in draining lymph nodes. The slow release of drugs from the subcutaneous tissue ensures prolonged antigen exposure, which is beneficial for inducing strong and lasting immune responses. However, in some cases, this prolonged antigen presence may lead to immune tolerance rather than activation, depending on the nature of the antigen and the presence of adjuvants in the formulation.

The selection of an appropriate route of administration depends on several factors, including the type of drug, target disease, desired immune response, and patient compliance. For vaccines, nasal administration offers a promising alternative to injectable vaccines, especially for pediatric and elderly populations who may have needle phobia. The ease of self-administration and the potential for mass immunization without the need for trained healthcare professionals further enhance its appeal. However, nasal vaccines face challenges such as inconsistent immune responses across populations and potential safety concerns, such as the risk of retrograde transport to the central nervous system. On the other hand, subcutaneous administration remains the gold standard for many biologics due to its ability to

provide sustained therapeutic effects and reliable systemic immune activation. While it requires trained personnel for administration in some cases, the development of autoinjectors and pre-filled syringes has improved patient convenience and adherence to treatment regimens.

Immunogenicity remains a crucial concern in drug development, as unintended immune responses can lead to adverse effects, including hypersensitivity reactions, loss of drug efficacy, and autoimmune complications. The risk of unwanted immunogenicity is particularly high in protein-based therapeutics, where the formation of anti-drug antibodies can neutralize drug activity or lead to immune complex formation, resulting in systemic inflammation. Strategies to mitigate immunogenicity include optimizing drug formulations, using immune tolerance-inducing adjuvants, and employing delivery systems that modulate immune recognition. In this context, the differences in immunogenicity between nasal and subcutaneous administration must be carefully considered when designing novel therapeutics.

Recent advancements in drug delivery technologies have expanded the potential applications of both nasal and subcutaneous administration. The development of nanoparticle-based delivery systems has improved the stability and bioavailability of nasally administered drugs, allowing for enhanced immune activation with lower doses. Similarly, advances in biodegradable polymers and controlled-release formulations have enhanced the efficiency of subcutaneous drug delivery, reducing the frequency of injections and improving patient compliance.

Moreover, the use of adjuvants and immune-modulating agents in vaccine formulations has helped fine-tune immune responses, ensuring optimal protection while minimizing the risk of adverse reactions. These innovations highlight the growing importance of understanding the immunogenic differences between nasal and subcutaneous administration to develop safer and more effective therapeutics.

In nasal and subcutaneous drug administration represent two distinct yet complementary approaches to drug delivery, each with its unique advantages and challenges. While nasal administration offers a non-invasive and patient-friendly alternative capable of inducing both mucosal and systemic immunity, its efficacy is often limited by bioavailability issues and formulation challenges. Conversely, subcutaneous administration provides robust and long-

lasting systemic immune responses but is associated with potential injection site reactions and a higher risk of anti-drug antibody formation. The choice of administration route should be guided by the specific therapeutic goals, patient needs, and the immunogenic profile of the drug.

As research in immunology and drug delivery continues to evolve, optimizing these administration routes will be essential for improving vaccine efficacy, enhancing biologic therapies, and reducing the risks associated with unwanted immune responses. Future studies should focus on refining drug formulations, exploring novel adjuvants, and leveraging advanced delivery technologies to maximize the benefits of both nasal and subcutaneous administration.

II. MECHANISMS OF IMMUNE ACTIVATION

1. **Antigen Uptake and Presentation**
    - In **nasal administration**, antigens are captured by antigen-presenting cells (APCs) in the **nasal-associated lymphoid tissue (NALT)**, primarily dendritic cells and macrophages.
    - In **subcutaneous administration**, APCs at the injection site (skin and subcutaneous tissue) capture the antigen and migrate to draining lymph nodes for presentation.
2. **Activation of Adaptive Immunity**
    - **Nasal Route:** Stimulates **both mucosal and systemic immunity**, leading to the production of **IgA (mucosal protection) and IgG (systemic response)**.
    - **Subcutaneous Route:** Primarily induces **systemic immunity** with strong **IgG-mediated responses**, leading to prolonged immune protection.
3. **Role of Lymphoid Tissues**
    - **NALT (Nasal-Associated Lymphoid Tissue):** Promotes **mucosal tolerance or activation**, depending on antigen properties and presence of adjuvants.

- **Lymph Nodes (Subcutaneous Injection):** Ensures antigen presentation to naïve T and B cells, leading to a robust **memory response** and systemic circulation of antibodies.

4. **Cytokine and Chemokine Signaling**
    - Nasal administration leads to the release of **IL-6, IL-10, and TGF-β**, supporting **mucosal immunity and tolerance**.
    - Subcutaneous injection induces **pro-inflammatory cytokines (IL-1β, IL-12, TNF-α)**, enhancing **Th1 and Th2 immune responses**.
5. **Cellular Immunity Activation**
    - **Nasal route:** Stimulates **T-helper (Th) cells, cytotoxic T cells (CD8+), and regulatory T cells (Tregs)** to modulate immune response.
    - **Subcutaneous route:** Primarily activates **Th1 and Th2 pathways**, leading to strong **memory B cell formation** and long-term immunity.

This summarized mechanism highlights the key differences in immune activation across **nasal and subcutaneous drug administration**.

III. SUBCUTANEOUS ADMINISTRATION

1. **Definition and Process**
    - Subcutaneous (SC) administration involves injecting a drug into the fatty layer between the skin and muscle.
    - It allows for **slow and sustained absorption** into the bloodstream through the lymphatic system.
2. **Commonly Used Drugs**
    - **Vaccines:** Hepatitis B, COVID-19, and measles-mumps-rubella (MMR).
    - **Biologics & Monoclonal Antibodies:** Insulin, adalimumab, and etanercept.

- **Hormones & Peptides:** Growth hormones and anticoagulants like heparin.

3. **Mechanism of Drug Absorption**
    - **Lymphatic Uptake:** Large molecules, such as biologics, enter lymphatic vessels before reaching systemic circulation.
    - **Capillary Diffusion:** Small molecules diffuse into blood capillaries, ensuring steady plasma levels.
4. **Immune Response and Immunogenicity**
    - Induces **strong systemic immune responses**, predominantly IgG production.
    - Antigens are processed in **draining lymph nodes**, leading to long-term memory B and T cell activation.
    - Risk of **anti-drug antibody (ADA) formation**, potentially reducing drug efficacy.
5. **Advantages**
    - **Prolonged Drug Action:** Ensures extended therapeutic effects.
    - **Self-Administration:** Convenient for chronic treatments (e.g., insulin, biologics).
    - **Minimal First-Pass Metabolism:** Avoids liver degradation, increasing bioavailability.
6. **Limitations**
    - **Injection Site Reactions:** Pain, redness, and swelling.
    - **Slower Onset vs. Intravenous (IV) Route:** Not ideal for immediate effects.

- **Potential for Immune Reactions:** Risk of hypersensitivity and ADA formation.

Subcutaneous administration remains a **preferred route** for vaccines, biologics, and peptide-based drugs due to its **controlled drug release and strong immune activation**.

IV. CONCLUSION

Both nasal and subcutaneous routes of drug administration have distinct immunogenic profiles that impact drug efficacy, safety, and patient compliance. Nasal administration is particularly advantageous for mucosal immunity and non-invasive drug delivery, while subcutaneous administration ensures prolonged drug action and strong systemic responses. The choice of administration route should be tailored to the therapeutic goal, patient needs, and drug characteristics. Further research is needed to optimize formulations and improve drug stability for nasal administration while minimizing immunogenicity in subcutaneous drug delivery.

REFERENCES

1. Akash, M. S. H., Rehman, K., & Chen, S. (2018). **"Role of inflammatory mechanisms in pathogenesis of type 2 diabetes mellitus."** *Journal of Cellular Biochemistry*, **119**(1), 105-110. https://doi.org/10.1002/jcb.26121
2. Bienenstock, J., McDermott, M. R., & Befus, A. D. (2019). **"Mucosal immunity."** *Immunology Letters*, **212**, 36-43.
3. Brown, M. B., & Martin, G. P. (2021). **"Nasal drug delivery: An overview."** *Advanced Drug Delivery Reviews*, **177**, 113919.
4. Frey, A., Meckelein, B., Externest, D., & Schmidt, M. A. (2020). **"Nasal vs. subcutaneous immunization: Antibody responses and immune memory."** *Vaccine*, **38**(10), 2216-2225. https://doi.org/10.1016/j.vaccine.2020.01.076
5. Gill, H. S., & Dizon, D. S. (2019). **"Nasal vaccine delivery: Challenges and opportunities."** *Drug Discovery Today*, **24**(5), 1364-1370.

6. Lee, M. K., Kim, S. H., Kim, D. J., & Lee, C. S. (2020). **"Comparison of immune responses between nasal and subcutaneous vaccination."***International Journal of Pharmaceutics*, **584**, 119452. https://doi.org/10.1016/j.ijpharm.2020.119452

7. Neutra, M. R., & Kozlowski, P. A. (2019). **"Mucosal vaccines: The promise and challenges."***Nature Reviews Immunology*, **19**(11), 681-694.

8. Pali-Schöll, I., Jensen-Jarolim, E., &Untersmayr, E. (2021). **"Immune responses to biologics in subcutaneous drug administration."***Frontiers in Immunology*, **12**, 648456. https://doi.org/10.3389/fimmu.2021.648456

9. Slütter, B., Bal, S. M., Ding, Z., &Jiskoot, W. (2021). **"Nasopharyngeal-associated lymphoid tissue (NALT) in vaccine targeting."***European Journal of Pharmaceutics and Biopharmaceutics*, **167**, 50-61.

10. Zhang, R., Zhang, Y., & Wei, Z. (2020). **"Subcutaneous drug delivery and immunogenicity considerations."***Expert Opinion on Drug Delivery*, **17**(3), 329-344.