Novel Topical Therapeutics

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KEYWORDS

• Topical therapy • Implantable therapeutics • Drug-eluting stent
• Drug absorption • Drug-eluting polymer

Intranasal drug delivery is a rapidly expanding field with great potential for the management of local and systemic disease. A growing body of literature has focused on the use of topical therapies for the treatment of allergic and inflammatory sinusitis. These treatments offer the potential for the delivery of high concentrations of therapeutic agent directly to the effected area. Intranasal drug administration for systemic delivery has also gained attention because it offers an easily accessible, highly vascularized mucosal surface area coupled to a porous endothelial basement membrane with a high total blood flow per volume of tissue. These attributes allow for direct absorption into the blood stream with decreased enzymatic degradation relative to the gut or liver, avoidance of the first-pass effect, and the potential for enhanced patient compliance.[1] Although the goal of each of these strategies is fundamentally different, they must overcome a similar set of anatomic and physiologic obstacles to be successful. Current techniques include optimization of traditional delivery devices and physiochemical modulation of pharmaceuticals to improve absorption. However, novel drug delivery strategies that have the potential to dramatically alter the transnasal management of a host of local and systemic pathologies are currently in development.

DISTRIBUTION STRATEGIES: INTRANASAL CAVITY

Regardless of the choice of agent, the mechanism of action of all intranasal pharmaceuticals is predicated on successful delivery to the respiratory mucosa. Because of the complex geometry and dynamic air flow patterns of the sinonasal labyrinth, efficient and predictable drug delivery in an unoperated patient is a challenge. Multiple variables including particle size, flow rate volume, pressure, and spray angle have all been shown to have a significant effect on delivery.[2] The major mechanism of

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drug deposition relies on inertial impaction on the nasal mucosa while gravitational sedimentation and Brownian diffusion play secondary roles. As a result, particulate size and density affect the degree and site of deposition. Particles greater than 10 μm will tend to remain within the nasal vault whereas those smaller than 5 μm remain aerosolized and are absorbed in the lower airways.[1] Using a cast model, Saijo and colleagues[3] demonstrated that efficiency of intranasal particle deposition could be further increased not only by altering the size but also the flow rate of the application. As a result, most commercial nasal delivery sprays use a monodroplet dispersion system with particle sizes of 50 to 70 μm and flow rates between 7 and 20 L/min.[4] Despite these strategies, a significant volume of each dose is deposited in the anterior nasal vault where it is rapidly cleared, severely limiting its systemic or local pharmacologic efficacy (**Fig. 1**).

DISTRIBUTION STRATEGIES: PARANASAL SINUS

This significant drug loss confounds efforts to determine optimal dosing regimens for systemic distribution because the percentage of medication actually reaching the respiratory mucosa is variable and difficult to predict. The problem is further compounded when addressing intraluminal sinus disease, because the treatment may never reach the intended site of action even if it does penetrate the nasal cavity. Olson and colleagues[5] looked at the distribution of 40 mL of radiopaque contrast by computed tomography (CT) in 8 unoperated patients using a range of delivery methods, and found that contrast reached the sphenoid in only 1 of 8 patients. While contrast was seen in the frontal recess in 2 patients, there was no penetration seen within the frontal sinus itself. Regardless of the mechanism of delivery, estimates of luminal delivery in an unoperated patient are less than 5% of the total volume

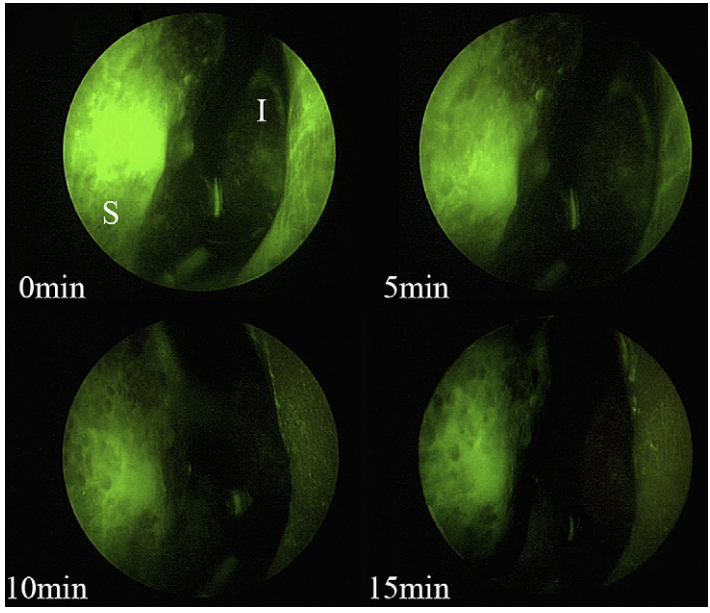

Fig. 1. Distribution and clearance of 120 mL of fluorescein-dyed saline administered by positive pressure irrigation bottle (S, septum; I, inferior turbinate). Note the predominant accumulation in the squamous portion of the vestibule and almost complete clearance of fluorescein from the inferior turbinate within 10 minutes.