Inhaled Insulin: Intrapulmonary or Intranasal?

Sweta Kumari, Danish Ahmed, Shruti Mishra, Shivangi Jaiswal.

Department of Pharmaceutical Sciences, Faculty of Health Medical Sciences Indigenous and Alternative Systems of Medicine, Sam Higginbottom Institute of Agricultural Technology and Sciences-Deemed University, Allahabad

Introduction

Initial attempts delivered the insulin hormone intramuscularly, intravenously, and eventually subcutaneously. Other routes of administration of the drug were explored. These included oral, nasal, sublingual, buccal, transdermal, vaginal, intramuscular, intrapulmonary, and intranasal delivery systems. The purpose of these latter studies was to determine a noninjectable method to deliver insulin to patients with type 1 and 2 diabetes that would effectively lower blood sugar, control hemoglobin A1c (in much later studies), and allow patients a simpler, less invasive, and more direct control oftheir underlying disease process. In January 2006 the United States Food and Drug Administration approved Exubera (Pfizer Pharmaceuticals, New York, NY) as the first pulmonary inhaled insulin. In actuality attempts to explore various methods to deliver insulin using intrapulmonary delivery had occurred since1925.

Summary

Insulin absorption can be obtained by many routes of administration dependent on the characteristics of the insulin molecule, its absorption enhancement promoters, formulation of the delivery system, nature of the system into which insulin is to be delivered, ease and convenience of administration, and cost. These factors suggest that, although intrapulmonary insulin administration is not currently available, intranasal insulin administration may be a more effective non-invasive method of administration.

Intrapulmonary Insulin

The lung has been considered a route for systemic delivery of many therapeutic proteins and peptides. This system includes two major anatomical parts. The first includes the upper airways, oral cavity, trachea, bronchi, and all upper airways distal to the bronchioles. The second includes the lower airways, conducting airways including respiratory bronchioles, alveolar ducts, and alveolar sacs. The lung offers a large surface area for drug absorption (w75 m2). The very thin alveolar epithelium (w0.1–0.5 mm thick) permits rapid drug absorption. The alveoli can be targeted for effective drug absorption by drug delivery by aerosol with a mass medium aerodynamic particle diameter <5 mm.

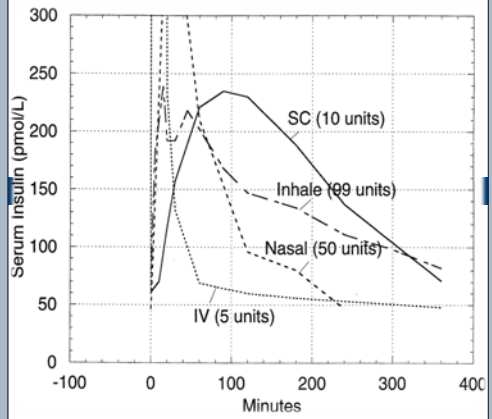


Fig 2: Comparison of Insulin delivery by different routes of administration.

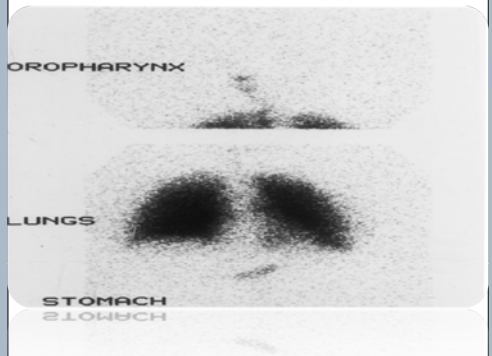
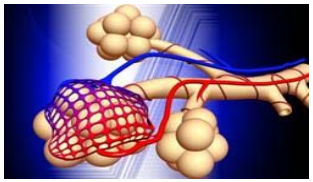


Fig 3: Gamma camera scans showing the deposition of the radioaerosol in the oropharynx (top) and lungs (bottom) of a patient with NIDDM

Pulmonary barrier and pulmonary absorption

Although alveolar and capillary epithelia may be highly permeable to water permeation of many hydrophilic substances, absorption of moieties of large molecular size and ionic species is limited. Molecular weight cutoff of tight junctions for absorption by alveolar type I cells is 0.6 mm, although endothelial junctions allow passage of larger molecules (4–6 mm)



After reaching the alveoli many proteins are degraded by proteases or are removed by alveolar macrophages that secrete short-lived peroxidases, inflammatory and immunomodulatory mediators [including granulocyte colony stimulating factor (GCSF), interleukins, leukotrienes, and proteases], and other host-defense molecules. These molecules degrade inhaled peptides and proteins.

Intranasal Insulin

Delivery of intranasal insulin, as with intrapulmonary delivery, is dependent on many anatomic and physiologic factors that enhance and inhibit absorption. These include nasal mucus concentration, character of the nasal mucus ,speed of mucociliary clearance, character and thickness of the mucociliary membrane, nasal mucus enzymes, macrophages, and other cells that may act as barriers to intranasal absorption and—groups of moieties not present in pulmonary secretions—xenobiotics, bacteria, fungi, and other active microbial and antimicrobial agents present in the nose that are not present in the lower airways or in lung

Advantages of Intranasal Insulin delivery

What makes intranasal insulin administration more attractive than intrapulmonary administration is that absorption into the nose not only bypasses gastrointestinal inhibition of insulin absorption but also offers two important physiologic processes for insulin absorption: 1) absorption by the large available complex plexus of small blood vessels in the nose and 2) absorption that is not limited by the blood–brain barrier and can pass directly into the brain. The former method of absorption was measured indirectly by comparing levels of endogenous insulin in blood, nasal mucus, and saliva under varying conditions

The Intranasal method of absorption, suggests that one aspect of these differences could relate to neural control of insulin metabolism through endogenous nasal absorption of insulin.

This hypothesis suggests that intranasal administration of insulin may offer a unique and useful method of insulin administration that may provide an important and novel method that could tap into important and heretofore unanticipated methods of control of insulin administration. This could not only control blood glucose directly but also control insulin effects on central nervous system (CNS) metabolism and secretion of substances by which insulin feedback mechanisms could be enhanced.

As with intrapulmonary delivery composition, the intranasal delivery system has been reported to play a significant role in insulin absorption. Intranasal absorption has been improved by using absorption enhancers such as aminoboronic acid derivatives, amastatin, and enzyme inhibitors . Surfactants, such as bile salts, have been reported to increase absorption by inhibiting the action of proteolytic enzymes present in nasal mucus . The variety of the composition of the intranasal delivery systems was reported to play a significant role in insulin absorption

Conclusion

The large surface area of the lung, its good vascularization, capacity for solute exchange and ultra thin membranes of alveolar epithelia are unique features that facilitate pulmonary insulin delivery. Large lung surface area (w75 m2) and thin alveolar epithelium (w0.1–0.5 mm) permit rapid drug absorption. First pass metabolism avoids gastrointestinal tract metabolism. Lung drug delivery depends upon a complex of factors including size, shape, density, charge and pH of delivery entity, velocity of entry, quality of aerosol deposition, character of alveoli, binding characteristics of aerosol on the alveolar surface, quality of alveolar capillary bed and its subsequent vascular tree. Intranasal insulin delivery faces a smaller surface area (w180 cm2) with quite different absorption characteristics in nasal epithelium and its associated vasculature. That makes the intransal insulin delivery more potent and efficacious than intrapulmonary insulin deliivery.

References

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