

Recent Developments in Intranasal Drug Delivery Technology are Creating New Vistas for Peptide and Protein Therapeutics.

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Introduction

From the time that insulin was first discovered and applied therapeutically to treat diabetes in the early twentieth century by Drs Banting, Best and Collip at the **University of Toronto**, proteins and peptides have held enormous attraction as potential therapeutic agents. Many peptides demonstrate high potency and high selectivity while exhibiting essentially no chemical toxicity owing to the fact that they are metabolised to naturally occurring amino acids. Counterbalancing the inherent chemical safety, high biological potency can make some otherwise beneficial peptides lethal at excessive or imprudent concentrations.

The combinatorial possibilities of peptide structure provide a nearly unlimited source of molecular diversity from which to select or screen for active compounds, which is yet another highly attractive attribute of peptides as potential therapeutics. Some naturally occurring peptides have direct therapeutic applications, for example, insulin, growth hormone, parathyroid hormone and calcitonin. Others may provide the initial biological activity from which new peptide and protein therapeutics may be designed. Important examples include a growing number of GLP-1 related peptides such as exendin-4 and similar molecules derived from non-human analogs of GLP-1 or native human GLP-1 itself, which promise to provide a new class of highly effective treatments for Type II diabetes and diabetes-associated obesity.

In spite of the many attractive aspects of peptides and proteins as potential therapeutic agents, their susceptibility to denaturation and hydrolysis in the gastrointestinal tract makes them unsuitable for oral administration, and this remains their major shortcoming as drugs. Therefore, while the range of clinical indications for therapeutic proteins and peptides is quite broad, (*Table 1*) the actual number of such therapeutics in general use today is quite small compared with the number of chemically synthesised and orally active pharmaceuticals currently on the market.

Patient Acceptance of Injectable Therapeutics Remains a Problem

Most of the peptide therapeutics listed in Table 1 are administered by injection (the few exceptions are footnoted). Injection is an inconvenient and expensive mode of administration. For situations where the medical consequences may not be immediate or life-threatening, and in cases where the administration must be frequent and chronic, patient noncompliance naturally becomes a serious issue. Extended half-life derivatives (i.e. via pegylation) and depot formulations of peptide and protein therapeutics, both still requiring injection, are partial but imperfect solutions and bring with them their own set of pharmacological problems and limitations.

For some peptide therapeutics, intranasal delivery has proven to be an acceptable route of administration. However, bioavailability, even for small peptides such as calcitonin (less than 4 kDa) which must be administered chronically on a daily basis for treatment of osteoporosis, is only about 3% on average. Nevertheless, the advantages of intranasal administration in terms of greater patient comfort, convenience, and elimination of needlestick injuries and syringe disposal concerns associated with daily injections, far outweighs the higher manufacturing costs resulting from poor bioavailability of current intranasal formulations. This is clearly evidenced by the commercial success of intranasal calcitonin which reportedly sells in excess of US\$400 M annually. From a technical perspective, however, success in intranasal delivery of peptides continues to be less than satisfactory, and the previously cited average bioavailability of 3% for calcitonin, with broad patient to patient variability ranging from 0.3% to 30.6% (Novartis Pharma, 2003), has actually been among the best performances for intranasal delivery of peptides.

Peptide or Protein	Clinical Indications
Arginine vasopressin ¹	Primary nocturnal enuresis; haemophilia A
Buserelin (LHRH analog)	Prostate cancer and endometriosis
Calcitonin ¹	Osteoporosis
Cetrorelix	Premature ovulation
Enfuvirtide	Antiviral (HIV fusion inhibitor)
Erythropoietin	Anaemia
Exendin-4/ GLP-1 related peptides ²	Diabetes
Ganirelix acetate	Infertility
G-CSF	Neutropenia
Glial Derived Neurotrophic Factor	Parkinson's disease
Glucagon	Severe hypoglycaemia
Goserelin acetate	Prostate cancer
Human Growth Hormone	AIDS wasting, dwarfism
Human parathyroid hormone (1-84) ²	Osteoporosis
Insulin	Diabetes
Interferon-alpha	Chronic hepatitis C; malignant melanoma
Interferon-beta	Multiple Sclerosis
Leuprolide	Prostate and breast cancer
LHRH	Control of ovulation
Melatonin	Sleep regulation
Nafarelin acetate ¹	Endometriosis
Nesiritide	Congestive heart failure
Octreotide	Growth hormone replacement
Oxytocin	Labour induction, milk secretion
Pramlintide acetate	Diabetes
PYY ²	Obesity
Somatostatin	Antisecretory in GI disorders
Teriparatide (1-34)	Osteoporosis
Triptorelin	Prostate cancer

¹ Currently available in intranasal formulation
² Completing clinical trials

Table 1 – Examples of current peptide and protein therapeutics now amenable to intranasal delivery

Advances in Intranasal Drug Delivery and Some Resulting Commercial Imperatives

Strong patient preference for intranasal drug delivery over injection – both for peptides and non peptides alike – has spurred growing interest in researching and developing improvements in efficiency of this mode of administration. These activities have taken two forms: direct high-throughput screening of compounds for improved intranasal absorption of peptides and proteins, and systematic optimisation of therapeutic-specific combinations of absorption enhancement agents. The global market for nasally delivered medications is valued at approximately US\$5 B; and growth of this segment is outpacing the growth of the overall pharmaceutical market, which in the US alone is estimated to be growing at 11% annually.

The advent of highly effective and non-irritating absorption enhancement agents affords a practical opportunity to reconsider the broad use of peptides as commercially and clinically viable human therapeutics. For companies with existing franchises in protein or peptide

therapeutics the benefits compound. Creation of intranasal formulations of existing injectable products provides access to new and expanded markets. Clinical data and experience generated in creating the injectable therapeutic can be directly applied in seeking regulatory approval of a 'new route of administration' for an already approved drug, shortening FDA approval times substantially.

'No injections' translates directly to greater patient acceptance and broader clinical indications. Sales of nasally-delivered therapeutics have demonstrated 5- to 12-fold increases in sales over the original equivalent injectable formulation. Many biopharmaceuticals, vaccines and peptides now given by injection could potentially be converted to intranasal products. Furthermore, offering multiple product forms affords a means to achieve maximum value extraction from an existing protein therapeutics franchise – through the classic marketing strategies of 'product proliferation and multilevel pricing'. And finally, at a time when many drug companies are facing expiration of key patents, new intranasal formulations of existing therapeutics can provide patent-life extension and facilitate product life-cycle management.

A New Class of Transmucosal Enhancement Agents for Peptide and Protein Drugs

A large number of molecules have been screened for the ability to enhance transmucosal delivery of peptides with limited success. Some of these are listed in Table 2. For the most part, these agents provide only a few percent bioavailability for peptide or protein drugs. By systematically optimising combinations of a few such enhancement agents on a therapeutic-specific basis, the bioavailability can be increased somewhat. However the percent bioavailability compared with injection typically remains in the single digit or low double digit percentages. Of greater concern, many of these agents are irritating and are toxic to nasal mucosa.

In recent years, development of a broad class of alkylsaccharide delivery enhancement agents – molecules that provide unsurpassed intranasal bioavailabilities,

Alkyl saccharides (various)	Polycarbophil cysteine
Aprotinin	Poly-L-Arginine
Benzalkonium chloride	Polyoxyethylene
Cetylpyridinium chloride	Polyoxyethylene-9-lauryl ether
Chitosan	Polyoxyethylene-23-lauryl ether
Chitosan-4-thiobutylamidine	Polysorbate 80
Cyclodextrin	Propylene glycol
Dextran sulfate	EDTA
Dodecyl azacycloheptyl-2-ketone	Sodium deoxycholate
Glycerol	Sodium glycocholate
Lauric acid	Sodium glycodeoxycholate
Lysophosphatidylcholine	Sodium lauryl sulfate
Menthol	Sodium salicylate
Methoxysalicylate	Sodium taurocholate
Methyloleate	Sodium taurodeoxycholate
Phosphatidyl choline	Sodium taurodihydrofusidate

Table 2 – Examples of molecules studied as transmucosal absorption enhancers.

comparable to those achieved by injection – was pioneered by Professors Elias Meezan and Dennis Pillion at the **University of Alabama** (Pillion *et al.*, 1994, and Pillion *et al.*, 1995). The resulting families of molecules, now patented and collectively designated as Intravail™¹ absorption enhancement agents, allow intranasal delivery – or more broadly, transmucosal delivery (Ahsan *et al.*, 2003) – of peptide, protein and non-protein macromolecular therapeutics (Arnold *et al.*, 2002) having molecular weights up to and in excess of 20 kDa, with bioavailabilities in excess of 50% compared with injection. These agents are non-toxic, non-irritating, chemically-synthesised molecules that are metabolized to CO₂ and H₂O (Weber and Benning, 1984). They provide controlled transient permeation of the nasal mucosal barrier with no or minimal irritation.

Equally important, the lack of toxicity or irritation of mucosal tissues has been demonstrated for a number of these molecules. For example, one Intravail agent, typically employed at 0.1% to 0.2% in intranasal formulations, has been shown to be non-irritating when tested at 25% in the rabbit eye model. The NOEL for this compound is approximately 20,000 to 30,000 mg per kg of body weight – roughly 1.4 to 2 kg for a 70 kg person. The World Health Organisation specified ADI (allowable daily intake) is approximately 15,000 times the amount that would be administered intranasally on a daily basis. If a patient were dosed daily every single day for 50 years, this would still amount to less than a single days ADI.

Figure 1 shows the intranasal bioavailability of protein and peptide therapeutics having molecular weights ranging from about 4 kDa to about 30 kDa (Arnold *et al.*, 2004). For peptides and proteins up to approximately 20 kDa, intranasal bioavailabilities in excess of 50%, compared with injection, can be attained. For smaller peptides, such as calcitonin, bioavailabilities in excess of 95% are observed. A number of clinically and commercially interesting peptide therapeutics in addition to calcitonin, such as exendin-4 and similar GLP-1 related peptides, PYY, teriparotide-PTH 1-34, and Leuprolide, among others, fall into this category.

¹ Intravail is a trade mark of Aegis Therapeutics LLC.

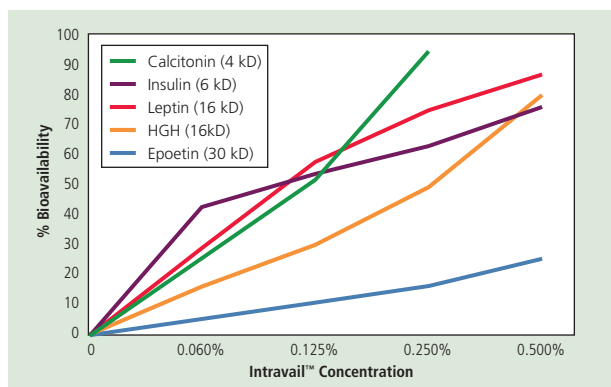


Figure 1 – Intranasal bioavailability compared with injection of equal amounts of protein and peptide therapeutics of different molecular weights up to 30 kDa as a function of Intravail enhancement agent concentration (data from Arnold *et al.*, 2004).

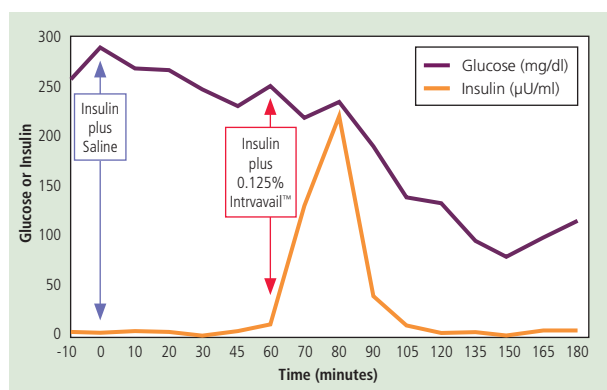


Figure 2 – Intranasal administration of insulin to a diabetic green monkey. Administration of insulin in the absence of Intravail at T₀ provides an internal control. In the presence of Intravail, systemic insulin levels rise and blood glucose levels fall into the normal range (Pillion and Meezan, unpublished observations).

The Intravail agents are inherently nondenaturing and are pharmaceutically compatible with virtually any peptide or drug – in some cases, such as insulin, offering dramatically extended protein stability (Hovgaard *et al.*, 1996).

Figure 2 shows the effectiveness of Intravail in the intranasal administration of insulin in a primate model of diabetes (Arnold, 2004; Pillion and Meezan, unpublished observations). In the absence of Intravail, essentially no insulin is observed to be absorbed systemically. After 60 minutes, a second administration of insulin in the presence of Intravail results in elevated systemic insulin levels and a reduction in blood glucose levels. These agents have been shown to dramatically increase transmucosal delivery and applications extend well beyond the intranasal route and include the ocular, oral and oral cavity, pulmonary, rectal, transdermal and vaginal routes of administration as well.

The essentially complete lack of intranasal absorption of insulin in the absence of Intravail has been confirmed in fluorescence microscopy studies. Figure 3, for example, shows the absorption of FITC-labelled insulin upon intranasal administration to the rat in the presence and absence of an Intravail absorption enhancer on subsequently sectioned rat nasal mucosa. Without the

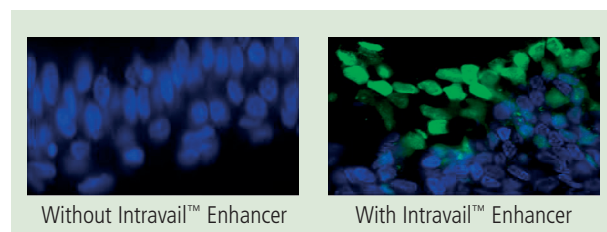


Figure 3 – The virtually complete lack of insulin absorption upon intranasal administration in the diabetic primate model described is confirmed by the lack of absorption of FITC-labelled insulin in the absence of Intravail as seen in these fluorescence light micrographs of vertical cross-sections of nasal septa excised from rats treated with FITC-insulin (Arnold *et al.*, 2004).

Intravil absorption enhancer, virtually no green colour arising from FITC-labelled insulin can be seen, whereas substantial absorption occurs when the Intravil enhancer is present.

The rapidly reversible and transient nature of the absorption enhancement effect of Intravil in the rat model has been studied in detail by Professors Meezan and Pillion. Reversibility is key to lack of irritation and patient tolerance. The intranasal absorption enhancement window for the 4 kDa peptide calcitonin is nearly completely closed beyond 120 minutes after administration of Intravil enhancer. For larger proteins such as somatropin at 22 kDa, the rapid reversibility is even more clearly evident in that virtually no somatropin enters systemic circulation if administered 60 minutes after administration of the Intravil enhancement agent (Pillion and Meezan, unpublished results).

Conclusions

Improvements in intranasal drug delivery, and in particular the development of novel, highly effective and non irritating transmucosal absorption enhancement agents for proteins, peptides and non peptide macromolecule therapeutics, which circumvent the two primary limitations of intranasal drug delivery in the past, namely mucosal irritation and poor bioavailability, are creating new commercial and clinical opportunities for major pharmaceutical and smaller biopharmaceutical companies alike. The recent advent of highly efficient transmucosal delivery enhancement agents offers many practical opportunities for drug companies to begin to embrace the broad use of peptides as commercially and clinically viable human therapeutics, and will soon offer patients new, more convenient, and more effective, therapeutic options across the broad spectrum of human diseases.

For companies with existing franchises in protein or peptide therapeutics, creation of intranasal formulations of existing injectable products provides a rapid path to regulatory approval and near term increased revenues. Revenues for intranasal forms of previously injectable-only therapeutics have historically expanded by 5- to 12-fold compared with the revenues for the corresponding injectable products, according to an analysis of IMS data by **Intranasal Technologies**. As key patents expire in the next few years, novel intranasal formulations of existing therapeutics can provide patent-life extension and should be an integral part of product life-cycle management.

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