

PHARMACOKINETIC AND PHARMACODYNAMIC APPLICATION TO THE USE OF PEPTIDES AND PROTEINS IN DRUG DELIVERY

Abstract

Proteins and peptides are fundamental components of biological systems, serving crucial roles in various physiological functions. The chapter reviews the essential functions that proteins and peptides perform in novel drug delivery systems, highlighting the variety of roles that these molecules play in biological systems as structural components, hormones, enzymes, and immunoglobulins. It describes the details of drug delivery systems and their various clinical applications. This topic also provides information regarding the use of pharmacokinetic and pharmacodynamic applications in therapeutics and diagnostics. These applications have an impact on dosage calculation, therapeutic monitoring in preclinical and clinical settings, and pharmaceutical development.

Keywords: Protein and peptides, Pharmacokinetics and Pharmacodynamic, Clinical and preclinical, Immunogenicity

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I. INTRODUCTION

Protein and peptide are naturally occurring large molecule have a significant and expanding role in novel drug delivery systems. Protein and peptides are the most abundant materials in living systems and biological cells. Its act as hormones, enzymes, structural elements, and immunoglobulin's. It is also important to participate in various metabolic processes, immunogenic defence, and biological activities.⁽¹⁾

II. PHARMACOKINETICAND PHARMACODYNAMIC PROPERTIES OF PROTEIN AND PEPTIDES

Peptide and protein drugs are not fundamentally different from conventional drug molecules but differ in complexity. The safe and effective use of any drug necessitates a thorough understanding of its pharmacokinetics and pharmacodynamic properties. The initial interrelationship between these processes and drug delivery, as well as the ultimate goal of rational disease treatment. Prior to the development of suitable drug delivery systems,

- A clinical pharmacological one in terms of the optimum rate and timing at which the drug should be administered; this calls for knowledge of the drug's concentration-effect profile in people and its dependence on the rate and time profile of drug input (e.g., continuous versus pulsatile or intermittent).
- A pharmaceutical-technical one in terms of the best system that can deliver the necessary rate and time specification via the preferred route of administration; this calls for knowledge of the capacity, flexibility, rate and time programming possibilities.

It is already quite difficult to find the appropriate answers to these two important questions for conventional delivery of drugs. This is even more true for peptide and protein drugs because they face a number of additional challenges both at the pharmacokinetic and dynamic levels. In general, peptides and proteins have high clearance properties and very short elimination half lives because they are rapidly degraded by peptidases, do not readily pass biological membranes and are generally relatively unstable in most biological fluids.⁽²⁾

III. ROUTES OF ADMINISTRATION OF PROTEIN AND PEPTIDES

Proteins and peptides can be administered through various routes, depending on the desired therapeutic effect, the specific molecule, and the intended target site. Here are some common routes of administration for proteins and peptides.

- Administration by Injection or Infusion
- Inhalational Administration
- Intranasal Administration
- Transdermal Administration
- Peroral Administration

Various elements, including the molecule's stability, size, target tissue, desired therapeutic effect, and patient-specific considerations, influence the choice of administration route.

1. Administration by Injection or Infusion: Proteins and peptides that are commonly administered through injection or infusion:

- **Intravenous (IV) Injection/Infusion**

- **Antibodies:** Monoclonal antibodies like bevacizumab (Avastin) and trastuzumab (Herceptin) are administered through IV infusion for the treatment of cancer.
- **Intravenous Immunoglobulin's (IVIG):** IVIG, a preparation of pooled antibodies from multiple donors, is administered through IV infusion for immune deficiencies and autoimmune disorders.

- **Subcutaneous (SC) Injection**

- **Insulin:** Patients with diabetes often self-administer insulin injections subcutaneously to regulate blood sugar levels.
- **Glucagon-like peptide-1 (GLP-1) agonists:** Drugs like exenatide (Byetta) and liraglutide (Victoza) used for the treatment of type 2 diabetes are administered via subcutaneous injection.

- **Intramuscular (IM) Injection**

- **Human chorionic gonadotropin (HCG):** HCG is administered through IM injection for various fertility treatments.
- **Vitamin B12 (cyanocobalamin):** Vitamin B12 deficiency is often treated with IM injections.

- **Intradermal (ID) Injection**

- **Tuberculosis (TB) skin test:** Tuberculin, a protein derivative, is administered via ID injection to screen for tuberculosis infection.

- **Intrathecal Injection**

- **Botulinum toxin:** Botulinum toxin injections are administered directly into the cerebrospinal fluid via intrathecal injection for the treatment of severe spasticity or dystonia.

- **Intraarticular Injection**

- **Corticosteroids:** Corticosteroids like triamcinolone are often injected directly into joints for the treatment of inflammatory conditions such as osteoarthritis.

2. Inhalational Administration: For localised or systemic effects, proteins and peptides are administered by inhalation directly into the respiratory system. Here are some illustrations of proteins and peptides that are frequently used in inhalation therapy:

Insulin Inhaled: Inhaled insulin is a type of fast-acting insulin that is administered through inhalation, such as Techno sphere insulin (marketed under the name Afrezza). It

is used by diabetics as a substitute for subcutaneous injections to control blood sugar levels.

- 3. Intranasal Administration:** Delivering proteins and peptides directly into the nasal cavity allows them to be absorbed through the nasal mucosa. This process is known as intranasal administration. Here are a few illustrations of proteins and peptides that are frequently administered orally.

Oxytocin: A peptide hormone called oxytocin can be given intranasally for a variety of reasons, such as to induce labour, increase lactation, and treat a few social and psychiatric conditions. Direct bloodstream absorption into the body is made possible by intranasal oxytocin, which has been shown to affect social behaviour and bonding.

- 4. Transdermal Administration:** Proteins and peptides can be administered transdermally, or through the skin, for systemic absorption. Although transdermal delivery is frequently used for small lipophilic molecules, proteins and peptides are difficult to deliver because of their size and hydrophilicity. Transdermal delivery technologies are still being researched and improved, though. For transdermal administration of proteins and peptides, the following strategies are being investigated:

- **Microneedles:** In order to improve the permeation of proteins and peptides, micro needle-based systems puncture the skin's outermost layer with tiny needles. For drug delivery, these microspores can either be solid or hollow. For the transdermal delivery of insulin, growth hormone, and other therapeutic peptides, micro needle patches have shown promise.
- **Nanoparticles and Liposomes:** Proteins and peptides can be shielded from enzymatic deterioration and made more easily permeable to the skin by being encapsulated in nanoparticles or liposome's. These delivery methods can improve trans dermal delivery by providing controlled release and better skin permeation.
- **Transferosomes:** Transferosomes are specialised lipid-based vesicles made to improve the way drugs penetrate the skin. The efficient delivery of proteins and peptides is made possible by their flexibility and ability to deform to pass through the skin's pores.

- 5. Peroral Administration:** Proteins and peptides are delivered through the gastrointestinal tract for systemic absorption through peroral administration, also referred to as oral administration. While the oral route is practical and frequently chosen by patients, proteins and peptides encounter difficulties because of their susceptibility to enzymatic degradation and poor intestinal absorption. To improve oral bioavailability, however, ongoing research projects and specialised formulations are being developed. In order to administer proteins and peptides orally, the following strategies are being investigated.

- **Anti-Protease Agents:** Proteins and peptides can be shielded from digestive tract enzymatic degradation by protease inhibitors. Increased oral bioavailability can be achieved by decreasing the degradation of the administered protein or peptide by inhibiting the activity of digestive enzymes like proteases.

- **Nanoparticles and Micro particles:** Encapsulating proteins and peptides in nano particles or micro particles can improve their stability and protect them from enzymatic degradation. These particles can also enhance the absorption of the protein or peptide by facilitating their transport across the intestinal epithelium.
- **Carrier-Mediated Transport:** Using carrier molecules recognised and taken up by specific transporters in the intestinal epithelium can improve protein and peptide absorption. This method can use natural uptake mechanisms in the gastrointestinal tract to improve oral absorption of these molecules.

IV. ADMINISTRATION ROUTE AND IMMUNOGENICITY OF PROTEIN AND PEPTIDES

The route of administration of proteins and peptides can affect their immunogenicity, which refers to a substance's ability to elicit an immune response in the body. Immunogenicity is an important factor to consider when developing and using protein and peptide therapeutics.

1. Subcutaneous, Intramuscular, And Intravenous Injection Routes

- **Immunogenicity:** Because the protein or peptide is introduced directly into the body via injection, it can elicit immune responses. Foreign proteins can activate the immune system, causing antibodies to be produced against the therapeutic molecule.
- **Mitigation Strategies:** Protein and peptide therapies administered via injection routes may be formulated to minimise immune recognition to reduce immunogenicity. Techniques such as PEGylation (the attachment of polyethylene glycol molecules) or modifying the structure of the molecule can help reduce immunogenicity.

2. Inhalational and Intranasal Routes

- **Immunogenicity:** Inhalational and intranasal routes generally have lower immunogenicity compared to injection routes. The respiratory mucosa has a different immunological environment compared to other tissues, resulting in reduced immune responses.
- **Mitigation Strategies:** While immunogenicity is generally lower with inhalational and intranasal routes, formulation optimization may still be necessary to minimize immune responses. Strategies such as encapsulation in nanoparticles or modification of the peptide sequence can help reduce immunogenicity.

3. Peroral and Transdermal Routes

- **Immunogenicity:** Comparing injection routes to transdermal and oropharyngeal routes, immunogenicity is typically lower. Barriers like the skin and digestive system can prevent the immune system from recognising certain proteins and peptides.
- **Mitigation Techniques:** However, problems with enzymatic degradation or subpar absorption may still arise with transdermal and peroral administration of proteins and peptides. Bioavailability can be increased and immunogenicity can be decreased by using formulation technologies like permeation enhancers or protease inhibitors.

The immunogenicity of a protein or peptide, a patient's unique characteristics, and the therapeutic setting can all have an impact. While every effort is made during the drug development process to reduce immunogenicity, it is still crucial to closely monitor patients for immune reactions and conduct regular evaluations of safety and efficacy.^{(3),(4)}

V. PHARMACOKINETIC AND PHARMACODYNAMIC APPLICATION TO THE PROTEIN AND PEPTIDE

Pharmacokinetics and pharmacodynamics are essential concepts in pharmacology that describe how drugs interact with the body, including how they are absorbed, distributed, metabolized, and eliminated (pharmacokinetics), as well as how they produce their effects at the target site (pharmacodynamics). Let's explore these concepts and provide an example for a protein and a peptide drug.

1. Diagnostic Application

- **Preclinical Application:** In order to understand how proteins and peptides behave and what effects they have in preclinical models, preclinical diagnostics must take into account their pharmacokinetic and pharmacodynamic properties. Here are some instances of preclinical diagnostic applications involving the pharmacokinetics and pharmacodynamics of proteins and peptides.⁽⁵⁾

➤ Pharmacokinetic Studies

- Absorption, Distribution, Metabolism, and Excretion (ADME) In order to understand how proteins and peptides are absorbed, distributed throughout tissues, metabolised, and eliminated, preclinical studies evaluate their ADME properties. By predicting their behaviour in humans, this information aids in choosing the proper dosage regimens.
- A therapeutic peptide's oral bioavailability, tissue distribution patterns, metabolism, and clearance rates, for instance, may be studied in preclinical studies using animal models.

➤ Pharmacokinetic Modelling and Simulation

- To forecast and simulate the time course of protein or peptide concentrations in different tissues or bodily fluids, preclinical pharmacokinetic models are created. This aids in improving dosing plans and evaluating the connection between dose and systemic exposure.
- A protein therapeutic's plasma concentration-time profile can be predicted using pharmacokinetic modelling, which can be used to guide the choice of the best dosing schedules and schedules for preclinical studies.

➤ Target Engagement Studies

- Preclinical studies assess the interaction between a protein or peptide therapeutic and its intended target(s) in preclinical models. This helps confirm target engagement and evaluate the relationship between target occupancy and pharmacodynamic effects.

- A preclinical study may use imaging techniques or biomarker analysis to assess the binding and engagement of a protein or peptide therapeutic with its target protein in specific tissues or cells.⁽⁶⁾
- **Clinical Application:** Clinical diagnostics must take into account proteins' pharmacokinetic and pharmacodynamic properties. Examples of their pharmacokinetic and pharmacodynamic clinical diagnostic applications are provided below
 - **TDM:** Therapeutic Drug Monitoring In order to ensure therapeutic efficacy and optimise dosage while avoiding toxicity, TDM entails measuring the concentration of a protein or peptide therapeutic in a patient's blood.
 - **Anti-TNF Biologics:** In order to keep therapeutic drug levels within the effective range, TNF inhibitors, such as infliximab (Remicade) and adalimumab (Humira), used for inflammatory diseases like rheumatoid arthritis or Crohn's disease, are monitored.
 - **Antiretroviral Therapy (ART):** To ensure effective viral suppression, drug concentrations for protease inhibitors and integrase inhibitors used to treat HIV, such as atazanavir and raltegravir, must be monitored.
 - **Immunogenicity Evaluation:** Patients may develop antibodies against the therapeutic agent as a result of immune responses induced by protein and peptide therapeutics. Evaluation of immunogenicity assists in assessing the emergence of anti-drug antibodies (ADA) and their potential influence on therapeutic efficacy.
 - **Anti-drug Antibody Testing for Biologics:** Patients receiving monoclonal antibody treatments such as rituximab (Rituxan) or adalimumab (Humira) are checked for the presence of anti-drug antibodies that could affect their response to treatment or result in negative side effects.
 - **Growth Hormone Therapy:** To ensure treatment effectiveness and adjust dosage as necessary, patients receiving growth hormone therapy are monitored for the emergence of antibodies against exogenous growth hormone.
 - **Pharmacodynamic Biomarkers:** Proteins and peptides can be used as pharmacodynamic biomarkers to track the biological response to or effect of a therapeutic agent. These biomarkers' measurement can offer information about a disease's development or how well a treatment is working as:
 - **Diabetes Management Using HbA1c:** Glycated haemoglobin (HbA1c) is used as a pharmacodynamic biomarker to evaluate long-term blood sugar control in diabetic patients, assisting in the improvement of treatment.
 - **Serum Creatinine** levels are used as a pharmacodynamic biomarker to assess kidney function in people who are taking nephrotoxic medications or who have renal disorders.^{(5),(6)}

These illustrations show how proteins and peptides are used in clinical diagnostic tests for pharmacokinetics (drug monitoring, immunogenicity evaluation), pharmacodynamics (measuring biomarkers), and pharmacodynamics-related problems. Treatment regimen optimisation benefits from knowledge of the pharmacokinetic and pharmacodynamic profiles of protein and peptide therapeutics to personalize therapies, and ensure patient safety and efficacy.

2. **Treatment Application:** Let's look more closely at the therapeutic uses for protein and peptide drugs in terms of pharmacokinetics and pharmacodynamics.
3. **Pharmacokinetic Treatment Application:** Pharmacokinetics refers to the study of drug movement within the body, including processes such as absorption, distribution, metabolism, and elimination. For protein and peptide drugs, their large size and complexity can influence their pharmacokinetic properties.
 - **Route of Administration:** Protein and peptide drugs are often administered through injection because they are susceptible to degradation in the gastrointestinal tract if taken orally. Subcutaneous or intravenous administration is common for these types of drugs.
 - **Absorption:** Protein and peptide drugs may have varying rates of absorption depending on their chemical properties and the route of administration. For example, subcutaneous injection usually provides a slower and more sustained absorption compared to intravenous injection.
 - **Distribution:** Distribution of protein and peptide drugs can be influenced by factors such as their molecular size, charge, and ability to bind to plasma proteins. These drugs may have a relatively large volume of distribution due to their ability to distribute into interstitial spaces.
 - **Metabolism:** Proteins and peptides are susceptible to enzymatic degradation in the body, particularly by proteolytic enzymes. Metabolism can occur in various organs, including the liver and kidneys.
 - **Elimination:** Protein and peptide drugs are typically eliminated through renal clearance, either as intact molecules or as metabolites. Their clearance rates can vary widely, leading to differences in dosing frequency.

Since protein drugs are administered via injection, their pharmacokinetics involve factors like absorption, distribution, metabolism, and elimination, similar to small-molecule drugs. Peptide drugs can undergo different routes of administration, and their pharmacokinetics can vary accordingly. Some peptides may be rapidly degraded in the gastrointestinal tract if taken orally, necessitating alternative administration routes like injection.(7)

Example:

- **Insulin:** Insulin is a protein hormone used to treat diabetes. When injected subcutaneously, it is absorbed slowly into the bloodstream. The rate of absorption can be influenced by various factors like injection site, formulation, and individual patient characteristics.(8)

- **Exenatide:** Exenatide is a peptide drug used to treat type 2 diabetes. When administered subcutaneously, it is absorbed more efficiently compared to oral administration. It has relatively short half-life, which requires multiple daily injections to maintain therapeutic levels.

4. Pharmacodynamic Treatment Application: Pharmacodynamics is concerned with how drugs exert their effects on the body, particularly at the target site. For protein and peptide drugs, their pharmacodynamic actions often involve binding to specific receptors or molecules. Here are some examples of pharmacodynamic treatment applications:

- **Receptor Binding:** Many protein and peptide drugs act as ligands that bind to specific receptors on cell surfaces or within cells. By binding to these receptors, they can initiate or inhibit signalling pathways, leading to the desired therapeutic effect.
- **Enzyme Inhibition:** Peptide drugs can function as enzyme inhibitors. By binding to enzymes, they can modulate biochemical pathways and influence physiological processes. For example, some peptide drugs act as protease inhibitors to block the activity of specific enzymes.
- **Immuno modulation:** Protein drugs like monoclonal antibodies can target and modulate immune cells or molecules, leading to immune modulatory effects. This is particularly relevant in the treatment of autoimmune diseases and certain types of cancers.
- **Hormone Replacement:** Peptide drugs can mimic the actions of endogenous hormones by binding to hormone receptors and inducing similar responses. For example, insulin is used to replace or supplement natural insulin in individuals with diabetes.⁽⁹⁾

Example:

- **Leuprolide:** Leuprolide is a peptide drug used to treat hormone-responsive cancers like prostate cancer. It acts as a gonadotropin-releasing hormone (GnRH) agonist, binding to GnRH receptors in the pituitary gland. Continuous stimulation of these receptors leads to desensitization and, ultimately, decreased production of sex hormones, which can help in managing hormone-dependent cancers. (10)

VI. SUMMARY

Pharmacokinetic and pharmacodynamic considerations play a crucial role in the development, dosing, and therapeutic application of protein and peptide drugs. Understanding how these drugs are absorbed, distributed, metabolized, and eliminated helps optimize their therapeutic effects while minimizing adverse reactions. Additionally, knowledge of their pharmacodynamic actions allows for targeted interventions in specific disease processes.

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