# ADMINISTRATION OF INJECTABLE MEDICATIONS

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Salam Kadhim is a pharmaceutical scientist with experience in drug discovery and development of small molecule compounds, biologics, siRNA, and cannabinoids in the areas of oncology, HBV, cardiovascular, ocular, and neurodegenerative disorders.

## **Topic Overview**

Administration of injectables involves the injection of medications into body tissues. Injection by parenteral administration using specific techniques via different delivery routes has significant applications in disease epidemiology and established diseases. In these diseases, vaccination regimens with injectables are effectively applied against viral and bacterial infections. Medical treatment with injectables provides therapeutic benefits against established diseases, including cancer, infectious and immune disorders, cardiovascular, endocrine, metabolic, genetic, neurodegenerative, and other acute and chronic conditions. There are advantages and disadvantages to using injectables over orally administered medications. Administration of any injectable has the potential to cause adverse reactions that are mitigated with emergency response measures. This course provides insights into the use and future trends of injectables with the intent to promote understanding of their application in healthcare and home settings.

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**Credits**: 1 hour of continuing education credit

Type of Activity: Knowledge

Media: Internet

#### **Fee Information:** \$4.99

**Estimated time to complete activity:** 1 hour, including Course Test and course evaluation

Release Date: October 18, 2022 Expiration Date: October 18, 2025

**Target Audience:** This educational activity is for pharmacists.

**How to Earn Credit:** From October 18, 2022, through October 18, 2025, participants must:

- 1. Read the "learning objectives" and "author and planning team disclosures;"
- 2. Study the section entitled "educational activity;" and
- 3. Complete the Course Test and Evaluation form. The Course Test will be graded automatically. Following successful completion of the Course Test with a score of 70% or higher, a statement of participation will be made available immediately. (No partial credit will be given.)

**Learning Objectives:** Upon completion of this educational activity, participants should be able to:

- 1. **Describe** insights for the use of injectables in healthcare and home settings
- 2. **Compare** the type, delivery routes, and techniques of injectables
- Describe the applications of injectables in disease epidemiology, established diseases, and the emergency response measures to adverse effects
- 4. **Identify** the pros and cons of injectables compared to oral medications

## Disclosures

The following individuals were involved in the development of this activity: Salam Kadhim, PhD, Steve Malen, PharmD, and Susan DePasquale, MSN, PMHNP-BC. Salam Kadhim, PhD, was employed as a Senior Scientist, Preclinical Pharmacology at INMED PHARMACEUTICALS INC., Vancouver, B.C., from February 4, 2019 – July 1, 2022. As of July 1, 2022, he has had no relationship with INMED PHARMACEUTICALS. There are no conflicts related to this activity from his prior employment. There are no financial relationships relevant to this activity to report or disclose by any of the individuals involved in the development of this activity.

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## Introduction

The administration of medications by injection has been an emerging trend for the delivery of drugs to patients. Injectable use is dependent on drug delivery and formulation type to optimize performance. Injectables are becoming increasingly patient-friendly. The growing use of injectables is targeted to outpatient and home settings for treatments of chronic conditions.

## **Defining Injectables**

Injectable is defined as delivering a sterile aqueous medication into a person's body via a needle and syringe or via auto, jet injector device, injection pen, or cartridge. It is among the most common procedures in healthcare and home settings, with at least 16 billion administered worldwide.<sup>1</sup> While the existing use of pharmaceuticals is still heavily weighted to orally delivered medications, the emerging trends reveal a significant shift towards the use of injectables.<sup>2</sup> The vast majority, of injectables, around 95%, are administered in curative care or as a treatment for a specific condition. Vaccination accounts for approximately 3%, and the rest are used for other purposes.<sup>1</sup>

# **Types of Injectables**

Many molecule types of drugs and biologics are used as injectables.<sup>3</sup> These include but are not limited to the following:

- Macromolecules:
  - Peptides
  - Oligonucleotides
  - o Antibodies
  - Carbohydrates
  - o Proteins
  - o Polymers

- Small Molecules:
  - Small molecule drugs
  - siRNA, mRNA
- Cell therapy
- Gene therapy

# **Delivery Routes**

Medications are introduced into the body by several routes of administration. Oral mucosal administration of drugs is the delivery of drugs sublingually, supralingually, or placing the drug within the inner lining of the cheeks (buccal mucosa).<sup>4,5</sup> Oral mucosal administration of a drug is preferred if a drug shows a greater first-pass effect *after* oral delivery.<sup>4</sup>

Other routes of administration are intranasal, intraocular, otic instillation (the ear), intrathecal, intraspinal, and intra-articular.<sup>7,8</sup> Intrathecal administration involves injecting a drug into the fluid-filled space between the thin layers of tissue that cover the brain and spinal cord.<sup>9</sup> An intradermal injection is the delivery of a drug between the layers of the skin.<sup>10</sup> Drugs may also be delivered rectally or vaginally.<sup>11</sup> Drugs may be inhaled into the lungs through the mouth, or delivered through the mouth or nose by a nebulizer.<sup>12,13</sup>

Medications may be applied to the skin (cutaneous) for a local, topical effect, or for a systemic, body-wide effect.<sup>14</sup> A transdermal patch may be used to deliver medications through the skin for a systemic effect.<sup>14</sup>

The three most common injection routes are intravenous, subcutaneous, and intramuscular.<sup>6</sup> Injectables administered by parenteral injection include the following:

- Subcutaneous Injection (SC)
- Delivers medication into the layer of fat just under the skin. Common uses include the following:

- insulin for diabetes
- heparin, or blood thinners
- measles (MMR) and chickenpox (varicella) vaccines
- palliative care pain medications such as fentanyl and morphine
- home-administered drugs such as Dupixent and fertility medications
- Intramuscular Injection (IM): Delivers medication into a muscle. Common uses include the following:
  - o vaccines
  - select antibiotics *e.g.*, penicillin and streptomycin
  - corticosteroids for inflammation or allergic reactions
  - hormones, *e.g.*, testosterone and medroxyprogesterone
  - drugs to patients who cannot take medications through other commonly used delivery routes
- Intradermal Injection (ID): Delivers medication between the layers of skin. Common uses include the following:
  - allergy testing
  - tuberculosis (TB) screening
  - administration of influenza vaccine *e.g.*, Fluzone ID
- Intravenous Injection (IV): Delivers medication directly into a vein. Commonly used to deliver:
  - fluids and electrolytes
  - local and general anesthesia
  - pain medications
  - blood or blood products
  - nutrition to a malnourished person
  - iron to iron deficiency person
  - contrast dye for imaging

- steroid, *e.g.*, dexamethasone
- chemotherapy
- o antibodies
- o antibiotics
- Intrathecal Injection (IT): Delivers medication around the spinal cord. Common use includes pain control after surgery (*e.g.*, morphine, ziconotide, and baclofen)
- Intracerebroventricular Injection (ICV): Delivers medication into the central nervous system (CNS) and cerebral ventricles for drugs that do not cross the blood-brain barrier
- Intraosseous Injection (IOS): Delivers medication into the bone marrow. Common uses to treat
  - severe injuries from accident or fall
  - electrocution
  - medication overdose
  - childbirth complications
  - respiratory distress
  - prolonged or back-to-back seizures
  - accidental poisoning
  - o insulin shock
  - o stroke
  - cardiac arrest
  - patients in septic shock
  - local anesthesia delivery for complex dental procedures e.g., root canal
  - dispensing pain medication to terminally ill patients
- Intraocular or Intravitreal Injections (IO/IVT): Delivers medication directly into the eye. Common uses include age-related macular degeneration, diabetic retinopathy, and retinal vein occlusion.

# **Injection Techniques**

Injectables are classified in multiple ways, including the type of tissue being injected into, the location in the body where the effect is produced, the duration of the effect, and the applied injection techniques. All injectables administered by parenteral injection avoid the first-pass metabolism, which potentially affects absorption through the gastrointestinal tract. Depending on the formulation types and delivery techniques, the injectables can be prepared to prolong drug absorption from the injection site.

There are four main routes to administer injectables at the injection site: IV, SC, IM, and intradermal. Perry, *et al.* (2014) provide pictorial examples of the proper technique and angle for injecting by IV, SC, IM, and intradermal.<sup>15</sup>

# Applications

# In Disease Epidemiology

Epidemiology is the clinical area used to find the causes of health outcomes and diseases in populations. In epidemiology, the patient is the community, and individuals are viewed collectively. Epidemiology is the scientific, systematic, and data-driven study of the frequency, pattern, causes, risk factors of health-related states, and events in specified populations. The application of injectables in epidemiology is to control health problems by preventing illness and managing patients with developed diseases.<sup>16</sup>

The administration of injectables in disease epidemiology is an effective method for vaccine immunization against viral and infectious diseases that significantly reduces morbidity. At present, human injectable vaccines are used in the prevention of more than thirty infectious diseases.<sup>17,18</sup> Vaccination provides strong, broad public health benefits compared to other preventive and curative interventions.<sup>17,18</sup>

There are several types of injectable vaccines against viral and bacterial infections:<sup>18</sup>

- Inactivated vaccines
  - killed version of the pathogen (*e.g.*, Hepatitis A, Flu (shot only), Polio (shot only), Rabies).
- Live-attenuated vaccines
  - weakened (or attenuated) form of a pathogen (*e.g.*, Measles, mumps, rubella (MMR combined vaccine), Rotavirus, Smallpox, Chickenpox, Yellow fever)
- Messenger RNA (mRNA) vaccines
  - provide protection against COVID-19
- Subunit, recombinant, polysaccharide, and conjugate vaccines
  - specific components of the pathogen such as its protein, sugar, or capsid, *e.g.*, Haemophilus influenza type b, Hepatitis B, Human papillomavirus, Whooping cough (part of DTaP combined vaccine), pneumococcal and meningococcal diseases, shingles.
- Toxoid vaccines
  - toxins made by the pathogen (*e.g.*, Diphtheria, Tetanus).
- Viral vector vaccines
  - modified virus versions as carriers to deliver protection (*e.g.*, COVID-19, influenza, vesicular stomatitis virus, measles virus, and adenovirus).

## In Established Diseases

Injectable drugs and biologics are effective against established acute and chronic diseases. Cancer is the number one indication for injectables, followed by infectious and immune diseases. In the case of cancer, intravenous injectables account for about two-thirds of the pharmaceutical therapeutics, while subcutaneous ones account for less than a fifth. The situation is reversed for immune and endocrine indications, where subcutaneous dosing with injectables accounts for more than two-thirds of all the therapeutics. In total subcutaneous and intradermal dosing accounts for about 30% of the injectables.<sup>2</sup>

Many types of chemotherapeutic drugs, either alone or in combination, are used as injectables to treat cancer. Some examples of small molecule injectables include the following:<sup>19</sup>

- Alkylating agents
- Nitrosoureas
- Antimetabolites
- Antitumor antibiotics
- Topoisomerase inhibitors
- Mitotic inhibitors
- Corticosteroids
- Targeted therapeutics
- Hormone therapeutics
- Immuno-therapeutics

The most successful small molecule injectables for other clinical indications such as immune, endocrine, neurological, metabolic diseases include the following:

- Statins
- Antiplatelets
- Calcium channel blockers
- Antipsychotics

- Proton Pump Inhibitors (PPIs)
- Erythropoiesis-Stimulating Agents (ESAs)
- Angiotensin Receptor Blockers (ARBs)

The greater part of the injectables comprises macromolecules and biologics, at about three-quarters of the total, with molecules ranging in size from peptides to antibody therapeutics. The biologics administered by injection are large, labile, molecules sensitive to the gastric environment and are inconsistently absorbed following oral dosing. Similarly, these macromolecules are not candidates for transdermal administration. The rising acceptance of biologics is directly related to their selectivity and their potency against challenging medical conditions.

Autoimmune conditions such as arthritis, which had been treated symptomatically for decades, are now treated at a more mechanistic level with injectable biologics such as Humira, Remicade, and Enbrel. At the same time, several aggressive cancers are being managed with antibody-based biologics such as Rituxan, Avastin, and Herceptin, once again selectively targeted to specific biologic processes.<sup>2</sup>

## **Emergency Response to Adverse Effects**

An adverse reaction is an undesirable side effect that occurs after the administration of any injectable medication. It could occur via needle sharing as well as from unsafe practices during recreational drug use. When adverse reactions occur, they can vary from minor (*e.g.*, soreness, urticaria, low-grade fever) to serious complications, such as the following:

- respiratory failure
- cardiovascular collapse
- persistent or severe pain at the injection site
- redness, swelling, warmth, or signs of infection
- abscess or collection of pus at the injection site
- damage to underlying tissues
- injury to adjacent nerves

- bone injury or infection
- excessive bleeding, especially in people with bleeding disorders
- formation of a large blood clot at the injection site
- allergic reaction
- nausea, vomiting, or dizziness
- fainting

To minimize the likelihood of an adverse reaction to an injectable, including a vaccine, the following emergency response measures are followed:<sup>20-23</sup>

Reaction	Signs and Symptoms	Management
Localized	Soreness, redness, itching, or swelling at the injection site	Apply cold compress to the injection site. Give analgesic (pain reliever) or antipruritic (anti-itch) medication.
	Slight bleeding	Apply pressure and adhesive compress over the injection site.
	Continuous bleeding	Place a thick layer of gauze pads over site and maintain direct and firm pressure; raise the bleeding injection site (e.g., arm) above the level of the patient's heart.
Psychological fright, presyncope, and syncope (fainting)	Fright before injectable is given. Patient feels "faint" ( <i>e.g.</i> , light-headed, dizzy, weak, nauseated, or has visual disturbance)	Have the patient sit or lie down. Have the patient lie flat. Loosen any tight clothing and maintain an open airway. Apply cool, damp cloth to the patient's face and neck. Keep under close observation until full recovery.
	Fall, without loss of consciousness	Examine the patient to determine if injury is present before attempting to move the patient. Place

	Loss of consciousness	the patient flat on back with feet elevated. Check to determine if injury is present before attempting to move the patient. Place the patient flat on back with feet elevated.
Anaphylaxis	Skin and mucosal symptoms such as generalized hives, itching, or flushing; swelling of lips, face, throat, or eyes. Respiratory symptoms such as nasal congestion, change in voice, sensation of throat closing, stridor, shortness of breath, wheeze, or cough. Gastrointestinal symptoms such as nausea, vomiting, diarrhea, cramping abdominal pain. Cardiovascular symptoms such as collapse, dizziness, tachycardia, and hypotension.	Epinephrine is the first-line injectable for anaphylaxis, and there is no known equivalent substitute Optional: H1 antihistamines relieve itching and urticaria (hives). These medications do not relieve upper or lower airway obstruction, hypotension, or shock Optional: Diphenhydramine ( <i>e.g.</i> , Benadryl) oral Maintenance of the airway, oxygen administration, and intravenous normal saline. Monitor patient closely until emergency medical system arrives Record patient's reaction, all vital signs, medications administered including time, dosage, response

# **Pros & Cons: Injectables Versus Oral Medications**

## Injectables

Advantages

- Rapid and uniform absorption
- Rapid onset of the action
- Not absorbed in the digestive tract

- They can be administered at home and taken less frequently than oral, daily pills
- Long-lasting injectables prolong drug release
- Patient compliance problems are largely avoided

#### Disadvantages

- Penetration through the skin via a small puncture
- They may require the use of an appropriate injection technique
- Sterile precautions required
- Possible local and systemic adverse effects

## **Oral Medications**

#### Advantages

- Simple, convenient, safe
- Convenient for single, repeated, and prolonged use
- Self-administered and pain-free
- Economical
- No sterile precautions needed
- The danger of acute drug reaction is lower
- Special knowledge or supplies (syringes, needles) are not required.

## Disadvantages

- Not suitable for emergency as the onset of action is slower
- Can only be used in conscious patients.
- Requires patient compliance.
- Not suitable for:
  - unpalatable and highly irritant drugs
  - drugs that are destroyed by gastric acid and digestive juices
  - o drugs with extensive first-pass metabolism
  - patients with severe vomiting and diarrhea.

- Requires first-pass and is inefficient as absorption is incomplete.
- Changes in drug solubility can result from interactions with other materials present in the gastrointestinal tract.

# **Future Trends**

Injectables are likely to forgo simple aqueous formulations in favor of sophisticated nanoparticle and protein fusion technologies.<sup>24</sup> Moncalvo, *et al.* (2020) reviewed recent advances in nanosized delivery systems. The goal of these delivery systems is to improve the safety and efficacy of protein therapeutics.<sup>24</sup>

The future of injectables is directly linked to the expansion of biologics. Macromolecules delivered as injectables provide immense therapeutic benefits. Their specificity and selectivity offer new therapeutic options for a variety of challenging medical conditions. Injectable biologics spur innovation in terms of injection devices, formulations, and nanoparticle engineering. Novel long-acting injectables or depot delivery systems for antipsychotic, substance misuse and hormonal therapy can achieve sustained drug release over a long period of time.<sup>25</sup> Such injectables enhance product quality by decreasing dosing frequency, simplifying drug regimens, reducing the relapse rate of disease, and improving efficacy and treatment adherence.

Novel prefilled syringes and injection pens have facilitated outpatient and home settings injections. Syringe and cartridge-based injectables reduce the possibility of errors in preparing and administering subcutaneous injections and find application in the management of chronic conditions like diabetes, heart disease, Alzheimer's, and COPD.

Equally important has been the trend towards the adoption of new formulation technologies, ranging from polymer conjugation to protein fusion, that stretch out the interval between dosing and improves drug performance. The application of new formulations will improve the potency of the injectable vaccines to produce new types that could be used for immunization against COVID, Ebola, Novo, Marburg, Zika, and other unmet medical needs. Polyvalent vaccines consisting of combined antigens from different strains or serotypes of one or several pathogens in a single vector could provide concurrent immunity to both Flu and COVID. Injectable chemotherapeutics consisting of a combination of several drugs plus adjuvants will provide additional therapeutic benefits.

With the constant improvement in smart injectable devices, not just limited to subcutaneous treatments, it is likely that injectables will find future practical applications to include intramuscular and intravenous dosing options in outpatient settings.

## Summary

Injectable treatments are widely used as an alternative to orally administered medications and are becoming increasingly patient-friendly due to their rapid absorption and onset of action. They find application in disease epidemiology as vaccines and as therapeutics against many established diseases. The injectables comprise small-molecule drugs and large-size macromolecule biologics that are administered by different routes and techniques. Adverse reactions could occur following the administration of injectables, and these are mitigated by emergency response procedures. The pros and cons of injectable use over orally administered medications are compared. The future trend for injectables is optimistic and is linked to biologics, smart injectables devices, novel formulations, nanoparticles, and protein fusion technologies.

## Course Test

#### 1. Which of the following are injectables?

- a. Insulin pen
- b. Vaccine
- c. Chemotherapeutic drug
- d. All of the above

#### 2. Which of the following is not injectable?

- a. Insulin pen
- b. Vaccine
- c. Chemotherapeutic drug
- d. Amoxicillin Tablet

# **3.** Which of the following are symptoms of anaphylaxis during an adverse reaction?

- a. Fever
- b. Hives and itching
- c. Soreness at the injection site
- d. Slight bleeding at the injection site

#### 4. What is the most serious adverse side effect of injectables?

- a. Nausea
- b. Vomiting
- c. Dizziness
- d. Anaphylaxis

## 5. Some of the techniques used to administer injectables include

- a. Intramuscular
- b. Intravenous
- c. Subcutaneous
- d. All of the above

# 6. Which of the following is a live-attenuated vaccine?

- a. COVID-19
- b. Tetanus
- c. MMR (Mumps, Measles, Rubella)
- d. Influenza

# **7.** Future trends in injectables might include

- a. Vaccines against Ebola, Marburg, and Zika viruses
- b. Combo vaccine against Covid plus Flu
- c. Combo of injectable chemotherapeutics (two or more drugs)
- d. All of the above

# 8. Chemotherapeutic injectable drugs for cancer treatment do not include

- a. antipsychotics.
- b. alkylating agents.
- c. antimetabolites.
- d. immuno-therapeutics.

## 9. What are the advantages of injectables?

- a. Not absorbed in the digestive tract
- b. Rapid and uniform absorption
- c. Rapid onset of the action
- d. All of the above

## 10. What are the disadvantages of injectables?

- a. Sterile precaution required
- b. Penetration through the skin via a small puncture
- c. Possible local and systemic adverse effects
- d. All of the above

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