

Parenteral Drug Delivery

CHAPTER OUTLINE

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OBJECTIVES

1. Describe the different routes of parenteral delivery and the factors influencing the absorption of drugs from different injection sites.
2. Define parenteral drug delivery and describe its advantages over other routes of drug administration.
3. Describe the characteristics of parenteral dosage formulations.
4. Explain the purpose of components of parenteral formulations: vehicle, co-solvent, buffer, tonicity agent, preservative, protectant, surfactant, and antioxidant.
5. Differentiate among dosage formulations available for parenteral administration and explain how drug is released from various injectable preparations.
6. Examine the application of drug-targeting systems in parenteral drug delivery.
7. Describe the use of specialized parenteral delivery devices.

Overview of Parenteral Delivery

Parenteral delivery has been defined by the Center for Drug Evaluation and Research of the U.S. Food and Drug Administration (FDA) as the administration of a drug by injection, infusion, or implantation.¹ *Parenteral delivery* means introducing drugs into the body outside of the enteral route; that is, outside of the gastrointestinal tract.² This delivery route can also be used to administer drugs directly to specific body organs and tissues to produce a desired therapeutic effect at a target site while minimizing systemic side effects.

Common routes of parenteral administration are described in the following sections. Table 1 lists the routes of parenteral administration.

Common Routes of Parenteral Delivery

Intravenous Injection

Drugs administered by the intravenous (IV) route provide the fastest onset of action because they are injected directly into the systemic circulation, and there is no lag time or absorption phase for the drug. Drugs administered by the IV route exhibit 100% **bioavailability**.

The three most common methods by which drugs are delivered IV are IV bolus, continuous IV infusion, and patient-controlled analgesia.

- IV bolus is IV administration of a dose of a drug all at once, typically in a few minutes, within or into a vein or veins.
- IV drip or IV infusion is IV administration of a drug within or into a vein over a sustained period. For a drug with a narrow therapeutic range, IV infusion can control the amount of drug administered over a fixed time period by controlling the infusion rate. Loading doses are administered at the start of IV infusions for drugs that have long biological half-lives. This quickly achieves effective serum concentrations of the drug. Steady-state serum concentrations can be maintained by giving the drug as a continuous IV infusion at a constant rate over longer periods.³

Table 1.
Routes of Parenteral Administration*

Name	Definition/characteristics of administration
Epidural	Administration on or over the dura mater
Intra-articular	Administration within a joint
Intra-arterial	Administration within an artery or arteries
Intracardiac	Administration within the heart
Intracavitary	Administration within a pathologic cavity, such as occurs in the lung in tuberculosis
Intradermal	Administration within the dermis Injection is given into the dermal layer of the skin.
Intralymphatic	Administration within a lymph channel or node
Intramuscular	Administration within a muscle Injection is given into the muscle fibers of the upper arm or gluteal area.
Intraosseous	Administration directly within the marrow of a bone The needle is injected right through the bone and into the soft marrow interior.
Intraperitoneal	Administration within the peritoneal cavity
Intraspinal	Administration within the vertebral column. Refers to both epidural and intrathecal routes.
Intrathecal	Administration within the cerebrospinal fluid at any level of the cerebrospinal axis, including injection into the cerebral ventricles. Injection is into subarachnoid spaces.
Intravenous	Administration within or into a vein or veins Injection is given directly into the vein.
Intracerebro-ventricular	Administration within a ventricle of the brain
Intravitreal	Administration within the vitreous body of the eye
Subcutaneous	Administration beneath the skin; also known as hypodermic injection Injection is given below the epidermis and dermis layer of the skin.

*From Center for Drug Evaluation and Research.³

The preferred route for analgesics is a continuous IV infusion, because it produces less fluctuation in serum concentrations of the drug than do intermittent intramuscular (IM) injections.

- Patient-controlled analgesia is designed to deliver IV bolus doses in addition to a slow, continuous IV infusion.⁴ This method allows patients to self-administer analgesics as needed for breakthrough pain. The drugs most commonly delivered by

this route are narcotic analgesics such as fentanyl,⁵ methadone,⁶ and morphine.³

Drugs that are commonly administered by the IV route are analgesics, general anesthetics, antiviral agents, antibiotics, immunosuppressive agents, antifungal agents, antibacterial agents, antihypertensive agents, vasodilators, antiarrhythmic drugs, and chemotherapeutic agents.

The IV route is not without adverse effects. IV injections are administered directly into the venous circulation, and hence highly vascular and perfused organs, such as the heart, lungs, liver, and kidney, rapidly acquire the drug. In some cases, however, a sudden increase in serum drug concentration may lead to toxicity. This can be prevented by giving a slow IV bolus injection. Other drugs with poor aqueous solubility may precipitate from solution and produce an embolism. Proper selection of the diluent and slow IV administration allows for proper mixing of the drug in the circulation. Finally, some vehicles may cause adverse effects in pediatric patients. For example, phenobarbital sodium is dissolved in propylene glycol, which may cause hyperosmolality in infants.⁷ In addition, because the alcohol and aldehyde dehydrogenase pathway that metabolizes propylene glycol is not well developed in infants and children younger than 4 years, repeated use of IV injections containing propylene glycol can lead to toxicity.

Lipid-soluble drugs like diazepam can easily cross the blood-brain barrier and are effective when given by the IV route. However, lipid-insoluble drugs are ineffective when given by the IV route if the desired target site of action is in the brain. Thus, lipid-insoluble drugs often need to be administered by specialized routes of delivery that bypass the blood-brain barrier. These specialized routes include intraspinal and intracerebroventricular injection, which will be discussed later in this chapter.

Intramuscular Injection

Drugs that may be irritating to the subcutaneous (SC) tissues are administered via IM injection. The IM injection site is usually the deltoid muscle of the upper arm or the vastus lateralis muscle in the anterolateral aspect of the middle or upper thigh. A needle long enough to reach deep into the muscle must be used and should be inserted at an angle of 80 to 90 degrees. Because of the time required for the drug to become available from the muscle to the systemic circulation, IM injections have a longer time to onset of effect and

a longer duration of action than IV injections. The rate of absorption and extent of availability of drugs depend on biopharmaceutical factors such as formulation characteristics and the physiology of the injection site.⁸ IM injections are safer than IV injections; however, incorrect IM administration techniques can result in blood clots, scarring of the skin, abscesses, and nerve damage leading to paralytic conditions.

Different formulation and delivery strategies are used for the administration of water-insoluble drugs. Water-insoluble drugs are solubilized in solvents such as propylene glycol and mineral oil for injection. These nonaqueous vehicles stay at the site of injection and release the drug slowly, which results in prolonged serum drug concentrations and a longer duration of action. Sparingly soluble ionizable drugs prepared as solutions for injection must be buffered to physiologic pH.⁸ Precipitation of the drug may occur as a result of this change in pH. Absorption may be prolonged as the drug redissolves in tissue fluids.^{9,10}

Another factor affecting drug absorption is the blood flow to the injection site. IM injections given into the deltoid muscle in the arm are absorbed faster than gluteal injections. This difference is likely due to the increased blood flow in the deltoid muscle and lower blood flow in the gluteus maximus muscle, which has a high content of adipose tissue. Slower rates of absorption after gluteal injections were seen in a higher percentage of women than men.^{8,9,11} Moreover, the injection volume is limited depending on the site of administration. Large muscles like the gluteal muscle can effectively absorb 4 to 5 mL of injected solution, whereas smaller muscles like the deltoid muscle in the arm can absorb up to 2 to 3 mL.¹¹

IM injections are available in immediate-release formulations as well as depot formulations for sustained release. Examples of these formulations are described in the following sections.

Immediate-Release Intramuscular Injection

Water-soluble drugs are dissolved in aqueous vehicles and prepared as solutions for injection. On IM injection, they distribute into the circulation and release the drug rapidly. The usual onset of action is 30 minutes, and the duration of action depends on the drug's half-life. One example is thyrotropin alfa for injection (Thyrogen®), a sterile, lyophilized product that forms

a solution after reconstitution and is injected IM for immediate release.^{12,13}

Depot Formulations for Intramuscular Injection

Depot injections release the drug slowly and maintain serum drug concentrations for a longer duration. Depot injections are long-acting dosage formulations indicated for maintenance treatment rather than initiation of therapy. Depot formulations are available as oil-based injections (eg, fluphenazine enanthate and estradiol cypionate), aqueous suspensions (eg, penicillin G procaine and penicillin G benzathine, methylprednisolone acetate [Depo-Medrol®], and medroxyprogesterone acetate/estradiol cypionate [Lunelle®]), and microspheres (eg, leuprolide acetate [Lupron Depot®]).

An example of a long-acting depot formulation containing the drug in the form of salt is fluphenazine enanthate (Prolixin Enanthate® injection).¹⁴ It is indicated for the maintenance treatment of nonagitated patients with chronic schizophrenia. Fluphenazine enanthate is water insoluble and is therefore dissolved in oil. On IM administration, it forms a depot of the drug dissolved in oil.^{15,16} The drug is released slowly from the depot and enters the blood circulation. Dosing intervals vary from 2 to 6 weeks and are determined by the response of the patient to therapy.

An example of an aqueous suspension acting as a depot is penicillin G benzathine/penicillin G procaine suspension (Bicillin® C-R). The injection contains water-insoluble drugs suspended in an aqueous vehicle. It is a stabilized, long-acting aqueous suspension containing sodium citrate buffer and the suspending agents lecithin and carboxymethylcellulose (CMC). The active ingredients are hydrolyzed in the blood to penicillin. The slow absorption from the IM injection site and subsequent hydrolysis leads to prolonged serum levels of penicillin, which allows dosing every 2 to 3 days when repeated doses are needed.¹⁷

Encapsulating drugs in polymer matrices and biodegradable microspheres provides a way to maintain therapeutic levels of the drugs for a longer time. An example of a polymer-based microsphere system used in depot formulations is leuprolide acetate for depot suspension (Lupron Depot®). Lupron Depot® microspheres are indicated for IM injection and are available in a pre-filled dual-chamber syringe. The drug chamber contains leuprolide acetate, incorporated in a biodegradable polymer of polylactic acid and D-mannitol.¹⁸ The dilu-

ent chamber contains sodium CMC, water for injection, D-mannitol, polysorbate, and glacial acetic acid to maintain pH. The microspheres form a depot at the site of injection, and the drug is released slowly at a constant rate as a result of the hydrolysis of the polymer. Depending on the prescribed dose, Lupron Depot® can be injected once every 1 to 4 months.¹⁹ Other examples of microsphere formulations are discussed in detail in the section Polymeric Biodegradable Systems for Parenteral Administration.

Subcutaneous Injection

SC injections are given into the SC or fatty layer of tissue below the epidermis and dermis. These injections are also referred to as *hypodermic injections* because the drug is administered beneath the skin.¹⁸ SC injections are usually small-volume injections and are administered at an angle of 45 degrees to the skin. They can generally be self-administered and are easy to administer with minimum discomfort. Patient education regarding proper SC injection techniques is important to minimize infection and other local adverse effects.

Drugs are absorbed at a slower rate after SC injections than after IM injections because there is less blood flow to the fatty tissue below the skin than to the muscle. The rate of absorption also depends on the penetration coefficient and the amount of drug at the site.² Absorption takes place through the capillary wall in the connective tissue. Penetration of drugs into the connective tissue depends on the concentration gradient of drugs across the capillary wall and connective tissue, the area of the membrane exposed to the solution, and the distance of diffusion. Medications that are injected by this route include vaccines, heparins, insulins, growth hormone, and epinephrine.

Intradermal Injection

Intradermal (ID) injections are administered within the dermis layer of the skin,¹ the upper layer of the skin just below the epidermis. ID injections are very-small-volume injections (0.1 mL) and are used to deliver drugs to produce local effects. Examples of uses of ID delivery are injections for skin testing, antigen delivery to evaluate for allergic reactions, and administration of vaccines (eg, influenza vaccine).⁸ ID administration of vaccines has been shown to enhance immune response more effectively than SC administration.²⁰ Thus, the ID route may target lymph nodes more efficiently than the SC route.

Specialized Routes

Intrasynovial

Intrasynovial injection is administration of a drug directly into the synovial cavity of a joint.¹ This form of parenteral delivery is used for the treatment of inflammation in patients with rheumatoid arthritis and collagen vascular diseases. Drugs administered by this route include methylprednisolone acetate and triamcinolone acetonide, which are available as injectable suspensions. The duration of action is significantly increased when a drug is injected intrasynovially. Repeated injections, if given, are generally administered no more frequently than every 3 months.

Intra-Articular

Intra-articular injection is administration of a drug within a joint. Intra-articular administration of local anesthetics and adjuvants is an alternate method for postoperative analgesia. Patients who have undergone ligament reconstruction and experience moderate to severe postoperative pain can benefit from intra-articular injection of ropivacaine and morphine via a catheter in the knee joint. This approach decreases the need for supplemental IV morphine.²¹ For the first few hours after intrasynovial or intra-articular injection, local discomfort in the joint may occur, but this is rapidly followed by effective relief of pain and improvement of local function.

Intraspinal

Intraspinal delivery is administration of drugs directly into the vertebral column.¹ It includes epidural and intrathecal injection. With epidural injection, drug is delivered to the outside of the dura and not into the cerebrospinal fluid. Thus the clinical effects are more localized to the spinal cord. Drugs can be delivered by a single bolus injection or as a continuous infusion (Figure 1).²² Advanced primary or metastatic cancer pain, thoracic and lumbar pain, nerve root injuries, and neuropathic pain are treated with intrathecal injections and infusions of opioids, local anesthetics, clonidine, baclofen, and other drugs used for the treatment of chronic pain, cancer pain, and intractable spasticity.²³

Morphine sulfate extended-release liposome injection (DepoDur®) is a special liposomal dosage formulation injected into the epidural space.^{24,25} DepoDur® injection is a sterile, preservative-free suspension of multivesicular liposomes containing morphine sulfate present as a suspension in 0.9% sodium chloride solution. On epidural injection, the multivesicular liposomes release morphine

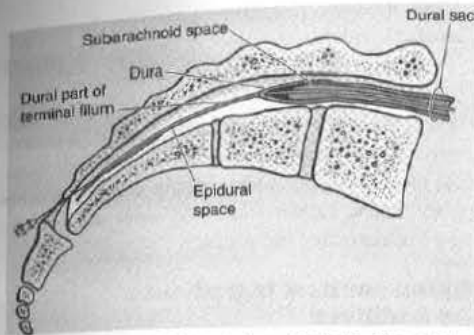


Figure 1. Anatomy of the spinal cord indicating the epidural space and the subarachnoid space. (Reprinted with permission from Moore and Dalley.⁹⁷)

systemically and into the intrathecal space through the meninges at a slow rate over a prolonged period.²⁶ When given as a single dose 30 minutes preoperatively, DepoDur® has produced persistent analgesia for 48 hours postoperatively. The distribution, metabolism, and elimination pattern of liposomal morphine sulfate is similar to that after delivery of other parenteral morphine formulations. DepoDur® is designed for single-dose administration and does not accumulate significantly in patients with impaired renal or hepatic function. Other examples of liposomal formulations are described in detail in the section on special IV delivery systems.

Intrathecal and Intracerebroventricular

Intrathecal injection is the administration of drugs within the cerebrospinal fluid at any level of the cerebrospinal axis, including injection into the cerebral ventricles.¹ When lipid insoluble drugs are needed to treat some neurologic disorders, it is necessary to bypass the blood-brain barrier and deliver drugs directly into the brain. This can be achieved by intrathecal administration, in which drugs are injected into the cerebrospinal fluid surrounding the spinal cord, or by direct injection of drugs into the brain by intracerebroventricular injection, which is an invasive approach.²⁷ Intrathecal injections can be given as a single dose or as continuous infusion via an indwelling catheter. Drugs that require long-term intrathecal infusion can be delivered by intrathecal catheters connected to an SC implanted infusion device. The intrathecal route is commonly used to deliver small lipophilic molecules for pain management. Opioid analgesics such as morphine, hydromorphone,

and fentanyl are effective when delivered by the intrathecal route.^{28,29}

Intracerebroventricular administration is commonly used for chemotherapy treatment of gliomas or for delivering neurotrophic factors to many areas of the central nervous system.³⁰

Intra-Arterial

The intra-arterial route is used to reduce drug exposure to the systemic circulation and to increase drug concentrations in the areas supplied by the artery into which the drug is injected. The intra-arterial route is used to deliver chemotherapeutic drugs such as cisplatin to treat head and neck cancer and to inject vasopressin to control gastrointestinal bleeding. New and safe angiographic techniques enable the placement of microcatheters into small arteries under direct vision using fluoroscopy.³¹ However, intra-arterial injections have been associated with embolism, occlusion of arteries, and drug toxicity.

Advantages and Disadvantages of Parenteral Delivery

The main advantages of parenteral delivery are the following:

1. It can be used in patients who are unable or refuse to take medications by mouth.
2. Rapid and complete absorption of drugs from the systemic circulation takes place if the drug is administered IV as a solution.
3. **First-pass hepatic metabolism** is avoided, which leads to improved bioavailability for drugs that undergo significant first-pass metabolism after oral administration.
4. Smaller doses can be used with IV administration than with oral administration.
5. The parenteral route avoids drug degradation in the gastrointestinal tract. A large number of proteins are administered parenterally.
6. IV administration of drugs has been shown to provide a more predictable pharmacokinetic and pharmacodynamic profile for drugs than oral administration.
7. The route of parenteral delivery can be tailored to the needs and condition of the patient. Direct injection of the drug by the IV route is beneficial in emergency situations when the need for therapeutic action is immediate. For a slower onset and a longer duration of action, drugs can be administered IM.

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