DOCTOR 2020 | JU

PHARMACOLOGY

WRITER : ALI ALMAHROOK

CORRECTOR : OMAMYMAH HILMI

DOCTOR: YACUOB IRSHAID

In the previous lecture we discussed two types of elimination: first order elimination and Zero-order elimination now we will continue the elimination:

Flow-Dependent Drug Elimination

- **Some drugs are cleared very rapidly by the organ of elimination (liver), so that at clinical concentrations of the drug, most of the drug per fusing the organ is eliminated on first pass of the drug through the organ.**
  - **Simply this elimination assumes that there are abundant enzymes that metabolize the drug in the liver, accordingly anything that reaches the liver through the circulation can be immediately eliminated.**
- **Rate of elimination is determined by the rate of hepatic blood flow.**
- **Drugs that have this property are called "high extraction ratio" drugs**.
- **Include morphine (**analgesic**), lidocaine (**local anesthetic**), propranolol (**beta blocker for ischemia in the heart**,** hypertension**), verapamil (**Ca+ channels blockers for hypertension**), and others.**

Recommended video for half-life,SS,LD from 25:10 to 49:23 from doc.fouda

https://youtu.be/NV5uiC7tt6o

Half-Life (t1⁄2) of Elimination

- **It is the time required for the amount of drug in the body or the plasma concentration of the drug (assuming first-order elimination) to drop by 50%.**
- **In this case (first order elimination) it is constant, and not related to dose.**
- **After ~ 4 half-lives, most of the drug will be eliminated from the body.**

Half-lives	% of drug removed
1	50
2	75
3	87.5
4	93.75

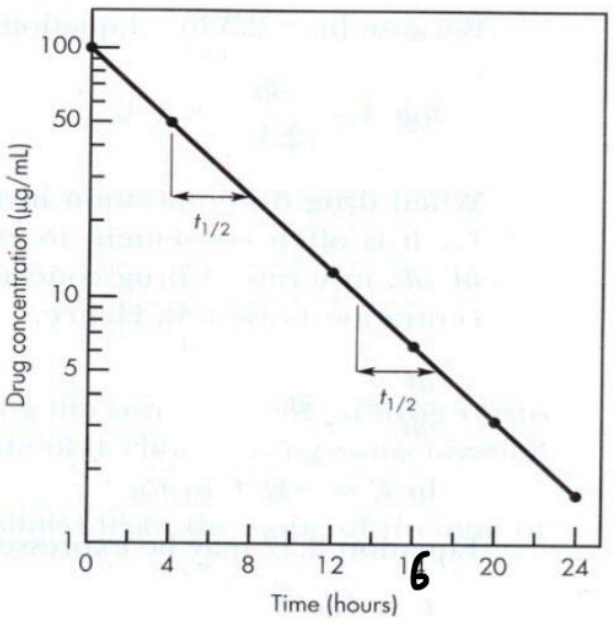
- **It is related to first-order elimination rate constant (k) such that:**
  - **k x t1⁄2 = 0.693**
    - (k) unit is per time and half-life unit is time so this eq. → no unit.
- **It is related to Cp (plasma concentration) for drugs undergoing zero-order kinetics, and is NOT constant.**
- **The higher the concentration, the longer the half-life of elimination and vice versa.**
  - Assume that we have a drug that undergo zero-order elimination and we gave a dose with 100ml and the body capacity to eliminate the drug is 5ml per hour so we need ten hours to reach 50ml concentration, thus the half-life equals **10 hours**, now assume that we gave the patient 20ml so we need two hours to reach 10ml concentration thus the half live is **two hours**!!!
  - In conclusion the half-life of **zero-order** elimination is **NOT CONSTANT** and it depends on the plasma concentration thus **increasing** the **concentration** will **increase** the half-life and vice versa.
  - ➢ But why this happens in the zero-order elimination??
  - ➢ Because zero-order elimination eliminate a constant amount per time not constant ratio like the first order elimination.

This is figure for a drug that follows first-order elimination:

We can calculate from this figure:

1-Half-life

2-Voulme of distribution (Vd)



3- First-order elimination rate constant (k).

4-The clearance (CL)

1- **For calculating the half-life take the concentration of the drug at time (4 Hours) it will be 50ml, and take the time when we reach 50% of the 50ml, so we will take the time when the concentration is 25ml and it will be 8 hours, thus the half-life is (8-4) =4 hours.**

Now take another points such as 10ml concentration and the time will be approximately 12.5 hours, then take the time we when reach 5ml and it will be approximately 16.5 hours thus the half-life is (16.5-12.5) = 4 hours!!!

And that proves that the first order elimination has a CONSTANT half-life

2- **For calculating the (Vd) use this mathematic eq.**

Vd= amount of drug in the body /plasma concentration

now the amount of drug in the body is known and the plasma concentration it's the concentration at time ZERO, but can we calculate a concentration at time zero??

No, we can't but we can calculate the concentration at any time so we calculate multiple points and since the first-order elimination is a linear plot so we draw the multiple points and extend the plot backward until we reach time zero.

للتوضيح أكثر احنا ما بنقدر نحسب تركيز الدواء في الدم عند الوقت صفر فعادي بنحسب اكثر من نقطة و بطلع معنا خط مستقيم فبنوصل الخط للوقت صفر و هيك بنعرف تركيز الدواء في الجسم عند الوقت صفر.

الوقت "صفر" هو تركيز الدواء أول ما يدخل الدم مباشرة مش بعد ثانية أو جزء من الثانية بس فش اشي اسمه وقت الصفر هذا الكلام نظري.

3- **For calculating first-order elimination rate constant (k).**

It's the slope of the linear plot or we can use this eq. (k*half-life=0.693).

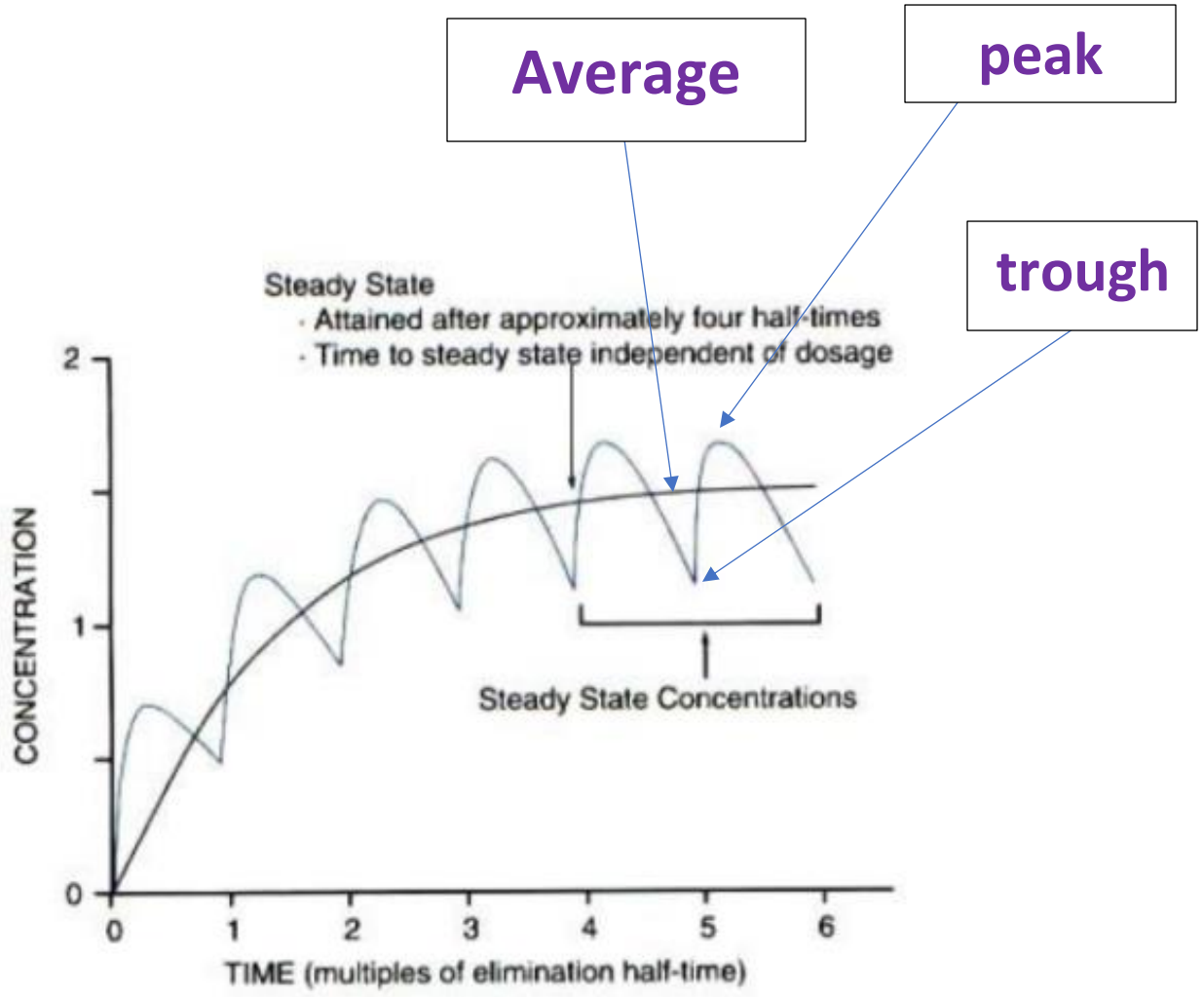
4- **For calculating the clearance (CL) by this eq.**

- **CL=k*Vd.**
- **Or this eq. (half-life=0.693*Vd/CL), remember (k) *half-life =0.693 thus (k) = 0.693/half-life.**
- **CL=(0.693/half-live) *Vd →→ (half-life=0.693*Vd/CL).**

Steady-State

When we are treating a disease the drug in the body should be in a constant concentration, to have a constant action and that what we mean by Steady-State.

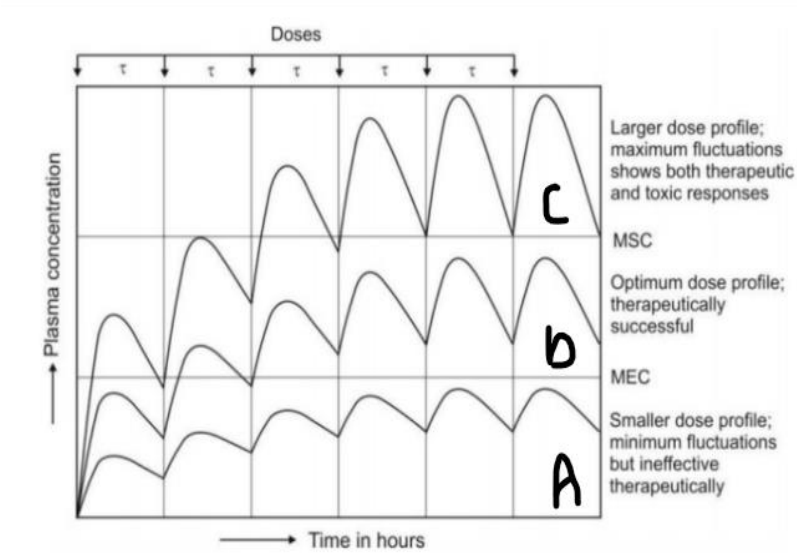
- **Steady-state is a condition achieved following repeated drug administration as occurs in clinical practice.**
  - **Notice here its impossible to have a Steady-State with a single dose, we need repeated drug doses.**
- **It occurs when the rate of drug administration (dosing rate) is equal to the rate of drug elimination.**
- **At steady-state, a constant peak, trough, and average drug concentrations are achieved.**
  - Average concentration **cannot** be calculated through (peak +trough)/two, it has another method not required from us.



- To reach the Steady-State we need a constant peak, trough, and average.
- **Steady-state is achieved after approximately 4 half-lives of repeated drug administration .why??(next page)↓↓**
- **50% of SS is achieved after one half-life of administration.**
- **Our aim during drug therapy is to attain a steady-state drug concentration (Css) within the therapeutic range, but NOT sub therapeutic or toxic.**

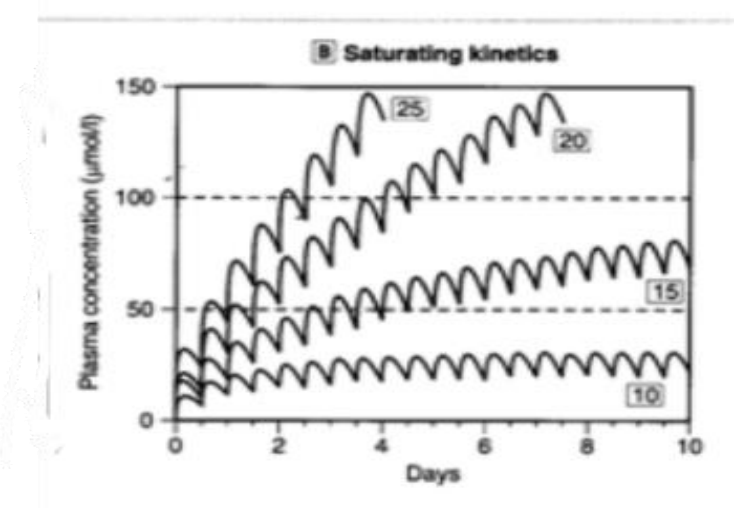
- **We enter the Steady-State Concentration after 4 half -lifes of repeated drug administrations, why??**
  - **Let's assume that we gave first dose 100ml and the half-life for the drug is 4 hours, now after 4 hours the concentration will decrease to 50ml and we gave a new dose so the concentration now is 150ml,after 4 hours the concentration we decrease to 75ml,we gave another dose the concentration became 175ml ,after 4 hours the concentration will decrease to 87.5ml approximately 90ml,we gave another dose the concentration become 190ml , after 4 hours the concentration will decrease to approximately 95ml approximately 100ml , give another dose the concentration become 200ml , after 4 hours the concentration we decrease to 100ml ,give another dose the concentration become 200 , after 4 hours the concentration we decrease to 100ml and so on…….**
  - **From this Scenario we notice that after 4 half-lifes the drug we enter the Steady-State Concentration (Css), rate of elimination = rate of administration**
  -

- **Our aim during drug therapy is to attain a steady-state drug concentration (Css) within the therapeutic range, but NOT sub therapeutic or toxic.**



Notice that we can enter the SS with a small dose but it will be effectiveness, because it's below the (**MEC**) minimal effective dose, also we can enter SS with a high dose which is toxic so our aim to be in the **therapeutic range (between MEC and MSC).**

We said that Steady-State is obtained after approximately 4 half-lifes and we explained why, and that's the case in first order elimination, now for Zero-order elimination its different and hard to obtain the Steady-State, why???



Simply the steady-state is Half-life dependent and since the zero order elimination half-life is NOT CONSTANT (also we explained why ↑↑page:2) we cannot predict the concentration of the drug if we increase the dose.

Now we have a problem, drug with long half-life like digoxin (1.5 day) we reach the steady state after 4 half-lifes (1.5*4) = 6 days, IS IT LOGICAL to keep the patient sub therapeutic (under MEC) for 6 days??

Of course it isn't logical, we should Load the dose to reach the SS early.

Loading Dose

- When the half-life is too long, steady-state will take a long time to be achieved.
- Therefore, we may need to give a loading dose to achieve drug concentration within the therapeutic range sooner (target concentration).
  - $LD = Vd. Css_{desired}$
  - $Css_{desired}$: target or therapeutic concentration.

Another problem will arise some drugs like digoxin with a Vd more than 1600L!!

To solve this problem, we divide the dose, if we have a 900ml dose we could divide the dose into 300ml every 3 hours in the same day, and by that we avoid the toxicity.

Maintenance Dose (MD)

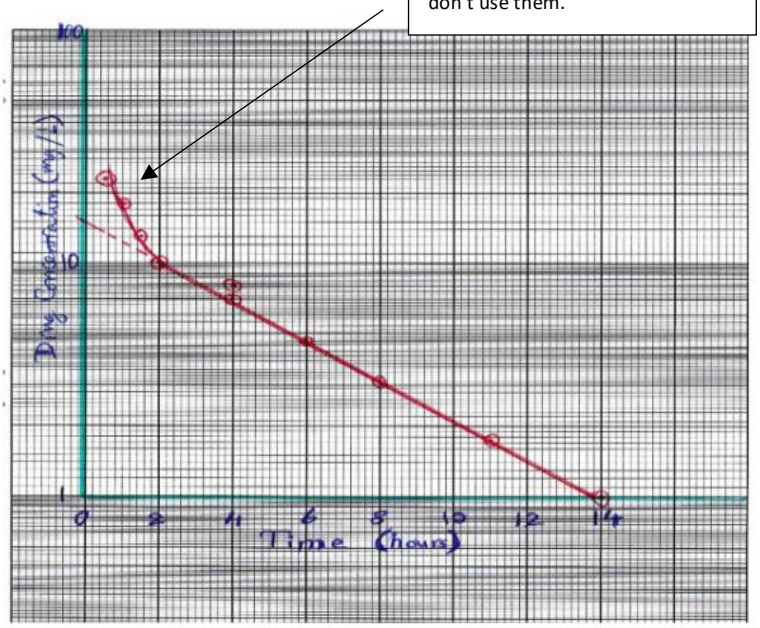
- **Simply it's the daily dose that we give the patient to compensate the loss of the drug so its clearance dependant.**
- **To attain and maintain a desired Css of a drug, we need to adjust the dose so that, the rate of drug administration is equal to the rate of drug elimination.**
- **Elimination is a function of clearance.**
- **MD = CL. $Css_{desired}$**

Case Scenario ↓↓↓↓

Case scenario

A volunteer was given a single 400 mg of a drug by IV injection. Serial blood samples were taken to analyze for drug level and construct a plasma concentration-versus-time curve.

The following semi-log plot of plasma concentration-versus-time was obtained



Results

Time (hours)	Drug concentration (mg/L)
0.5	23
1	18
1.5	13
2	10
4	7
6	4.7
8	3.1
11	1.75
14	1

الأجوبة بالأسفل

Q1-Which of the following is the approximate apparent volume of distribution of the drug?

A. 5 L

B. 10 L

C. 25 L

D. 50 L

E. 100 L

Q2 -What is the half-life of elimination of the drug?

A. 1.5 hours

B. 3.5 hours

C. 5.5 hours

D. 7.5 hours

E. 9.5 hours

Q3- Which of the following is the first-order elimination rate constant of the drug?

A. 0.0385 / hour

B. 0.0770 / hour

C. 0.1155 / hour

D. 0.1540 / hour

E. 0.1925 / hour

Q4- Which of the following is the clearance of this drug?

A. 1 L/hour

B. 2 L/hour

C. 3 L/hour

D. 5 L/hour

E. 10 L/hour

Q5- What is the maintenance dose every 24 hours if the steady-state therapeutic concentration of the drug is 10 mg/L?

A. 100 mg

B. 500 mg

C. 750 mg

D. 1000 mg

E. 1200 mg

6-Does this drug require a loading dose?

A. Yes

B. No

C. I do not know

If the answer is yes, calculate the loading dose.

1-C 2-B 3-E 4-D 5-E

6- https://youtu.be/7VFDucEVNwo

طريقة الحل "المتوقعة" السؤال الأول لازم نستخدم الرسم عشان نطلع تركيز الدوا عند الوقت "صفر"....سؤال 2 من الجدول بس بنهمل اول ثلاث معطيات لانهم لل distribution و الباقي تطبيق مباشر ع القوانين.

Routes of Drug Administration

A. Enteral (by the GI tract from above or below)
B. Parenteral (outside the GI tract specifically injections)
C. Others (neither Enteral nor Parenteral)

Enteral routes

1-Oral route (PO):

- The drug should be swallowed (with water to enhance the disintegration and dissolution).
- Most commonly used route.
- Safest, most convenient, and most economical
- Duodenum is the major site of absorption, but stomach, jejunum and ileum may be involved.

Disadvantages:

1. The patient must be cooperative (compliant).

2. Absorption is variable because of several factors affecting the rate and extent of absorption:

a) Vomiting

b) Failure of disintegration and dissolution

c) First-pass effect

d) Drug may be destroyed by gastric acid or intestinal flora.

e) Food may delay absorption (and vice versa for certain drugs).

f) Alteration in intestinal motility may affect absorption.

g) Absorption may be affected by splanchnic blood flow.

2. Sublingual route (SL):

- **Drug is placed under the tongue.**
- **Avoids first-pass effect (even its oral its effect as same as the IV).**
- **Used when a rapid onset is required – such as in angina pectoris.**
- **Not commonly used.**

3. Rectal route (PR):

- **Avoids first-pass effect partially (~ 50%). Why?**
  - **(the dose that we put in the rectum 50% of it will pass directly to the systemic circulation because its dependant on the blood supply to the rectum)**
- **Useful in unconscious or vomiting patients.**
- **Absorption is often irregular, incomplete and unpredictable.**
- **Can be used for a local effect.**
- **Used for drugs poorly absorbed from, or unstable in the GIT.**
- **Used for rapid effect.**
- **Aseptic technique is required.**

Parenteral Routes

1- Intravenous route (IV):

- **Bolus vs infusion.**
- **Only aqueous solutions may be injected IV.**
- **Rapid onset of action.**
- **Oily vehicles or those that precipitate blood constituents should NOT be given IV.**
- **No first-pass hepatic metabolism, the drug goes first to the right side of the heart, the lung, the left side of the heart, then to the systemic circulation.**

Disadvantages:

1. Produce high initial concentration of the drug that might be toxic.

2. Once injected, the drug is there…??

2-Intramuscular route (IM):

- **The drug is injected within muscle fibers of deltoid, gluteus maximus or vastus lateralis.**
- **Absorption of drug depends on blood supply (slower for g.m).**
- **Absorption is reduced in circulatory failure or shock.**
- **To be injected IM, the drug must be non-irritating to tissues**

Can utilize:

a. Aqueous solutions for fast absorption and rapid action.

b. Depot preparations and suspensions for slow or sustained absorption (oily vehicles or ethylene glycol).

- **Can accommodate large volumes.**

3-Subcutaneous injections (SC, or SQ):

- **The drug is injected under the skin.**
- **Absorption is affected by blood flow.**
- **Drug should be non-irritating to tissues.**
- **Absorption is slow and sustained.**
- **Accommodate smaller volumes than IM.**
- **Solid pellets can be implanted under the skin to produce effects over weeks-months**

Other Routes

1-Inhalational or pulmonary route:

- **Used for gaseous or volatile drugs, such as general anesthetics.**
- **Can also be used for solids that can be put in an aerosol, such as drugs for bronchial asthma.**

- **Drugs are absorbed across pulmonary epithelium and mucous membranes of respiratory tract.**
- **Absorption is rapid.**
- **Avoids first-pass effect.**
- **The lung acts as a route of elimination also.**

2-Topical application:

- **For a local effect on:**

a. mucous membranes: conjunctiva, nose, mouth, nasopharynx, oropharynx, vagina, rectum, colon, urethra, and urinary bladder.

b. skin: highly lipid-soluble drugs can be absorbed systemically.

- **Systemic absorption also occurs from abraded,**

burned and inflamed skin.

3-Transdermal route (TD):

- **The drug is applied to the skin for systemic effect, such as in angina.**
- **For a sustained effect.**
- **Avoids first-pass metabolism.**

Enteral Routes			
Buccal or sublingual (SL)	Rapid absorption from lipid-soluble drugs.	No "first-pass" effects. Buccal route may be formulated for local prolonged action. Eg, adhere to the buccal mucosa with some antifungal. Buccal is different from sublingual which is usually placed "under tongue."	Some drugs may be swallowed. Not for most drugs or drugs with high doses.
Oral (PO)	Absorption may vary. Generally, slower absorption rate compared to IV bolus or IM injection.	Safest and easiest route of drug administration. May use immediate-release and modified-release drug products.	Some drugs may have erratic absorption, be unstable in the gastointestinal tract, or be metabolized by liver prior to systemic absorption.
Rectal (PR)	Absorption may vary from suppository. More reliable absorption from enema (solution).	Useful when patient cannot swallow medication. Used for local and systemic effects.	Absorption may be erratic. Suppository may migrate to different position. Some patient discomfort.
Other Routes			
Transdermal	Slow absorption, rate may vary. Increased absorption with occlusive dressing.	Transdermal delivery system (patch) is easy to use. Used for lipid-soluble drugs with low dose and low MW (molecular weight).	Some irritation by patch or drug. Permeability of skin variable with condition, anatomic site, age, and gender. Type of cream or ointment base affects drug release and absorption.
Inhalation and intranasal	Rapid absorption. Total dose absorbed is variable.	May be used for local or systemic effects.	Particle size of drug determines anatomic placement in respiratory tract. May stimulate cough reflex. Some drug may be swallowed.

Table 13-1 Common Routes of Drug Administration

Route	Bioavailability	Advantages	Disadvantages
Parenteral Routes			
Intravenous bolus (IV)	Complete (100%) systemic drug absorption. Rate of bioavailability considered instantaneous.	Drug is given for immediate effect.	Increased chance for adverse reaction. Possible anaphylaxis.
Intravenous infusion (IV inf)	Complete (100%) systemic drug absorption. Rate of drug absorption controlled by infusion rate.	Plasma drug levels more precisely controlled. May inject large fluid volumes. May use drugs with poor lipid solubility and/or irritating drugs.	Requires skill in insertion of infusion set. Tissue damage at site of injection (infiltration, necrosis, or sterile abscess).
Subcutaneous injection (SC)	Prompt from aqueous solution. Slow absorption from repository formulations.	Generally, used for insulin injection.	Rate of drug absorption depends on blood flow and injection volume. Insulin formulaton can vary from short to intermediate and long acting.
Intradermal injection	Drug injected into surface area (dermal) of skin.	Often used for allergy and other diagnostic tests, such as tuberculosis.	Some discomfort at site of injection.
Intramuscular injection (IM)	Rapid from aqueous solution. Slow absorption from nonaqueous (oil) solutions.	Easier to inject than intravenous injection. Larger volumes may be used compared to subcutaneous solutions.	Irritating drugs may be very painful. Different rates of absorption depending on muscle group injected and blood flow.
Intra-arterial injection	100% of solution is absorbed.	Used in chemotherapy to target drug to organ.	Drug may also distribute to other tissues and organs in the body.
Intrathecal Injection	100% of solution is absorbed.	Drug is directly injected into cerebrospinal fluid (CSF) for uptake into brain.	
Intraperitoneal injection	In laboratory animals, (eg, rat) drug absorption resembles oral absorption.	Used more in small laboratory animals. Less common injection in humans. Used for renally impaired patients on peritoneal dialysis who develop peritonitis.	Drug absorption via mesenteric veins to liver, may have some hepatic clearance prior to systemic absorption.

تم بحمد الله