Heart Failure

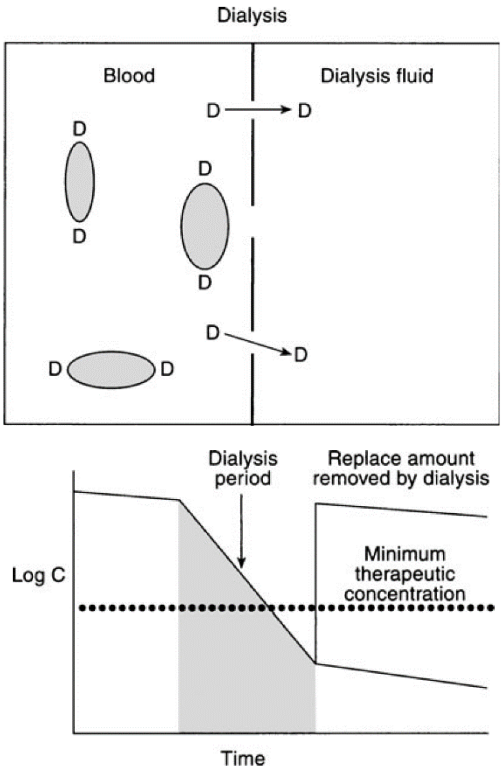
Heart failure is accompanied by a decrease in cardiac output which results in lower liver and renal blood flow. The most common consequences of heart failure on drug kinetics are:

1. Decrease in hepatic clearance, especially for compounds with moderate-to-high hepatic extraction ratios.
2. Decreased drug bioavailability due to the collection of edema fluid in the gastrointestinal tract which makes absorption of drug molecules more difficult and decreased blood flow to the gastrointestinal tract.
3. Decrease in the volume of distribution.

Dialysis

Dialysis is a process whereby substances move via a concentration gradient across a semipermeable membrane as described in the figure below.

Synthetic semipermeable membranes are used in **artificial kidneys** to remove waste products from the blood. Also, **physiologic membranes**, such as those present in the peritoneal cavity in the lower abdomen, can be used with **peritoneal dialysis** as an endogenous semipermeable membrane.



Substances that are small enough to pass through the pores in the semipermeable membrane will pass out of the blood into the dialysis fluid. Once in the dialysis fluid, waste products and other compounds can be removed from the body.

Dialysis is usually used for the removal of toxic waste products that would usually be eliminated by the kidney. Drug molecules are also removed from the blood coincidental to the removal of toxic waste products. In some cases, dialysis is used to remove drugs from the bodies of patients that have taken drug overdoses or are experiencing severe adverse effects from the drug. In both cases, dialysis will cause a decline in the plasma concentration of drug that are significantly removed by dialysis. This might cause a decline in the plasma concentration below the minimum therapeutic concentration and replacement dose will be required.

In a renal failure patient, the only clearance mechanism available to remove drugs from the body are nonrenal ($Cl = Cl_{NR}$, where Cl is total clearance and Cl_{NR} is nonrenal clearance).
In case of dialysis; $Cl = Cl_{NR} + Cl_D$, where Cl_D is dialysis clearance.

If dialysis clearance is ≥30% of total clearance then a replacement dose is required.

Drug Characteristics that Effect Dialysis Removal

1. Molecular Size

The semipermeable membranes used in dialysis are either

a. Low-flux filter; permit the permeation of small drug molecules (molecular weight <500 Da, such as theophylline, lidocaine, procainamide). Drug molecules with moderate molecular weights (molecular weight 500–1000 Da, such as aminoglycoside antibiotics [~400–500 Da] and digoxin) may have sufficient dialysis clearances to require postdialysis replacement doses.
b. High-flux filters; permit the removal of large drug molecules such as vancomycin.

2. Water/Lipid Solubility

Drugs that have a high degree of water solubility will tend to partition into the water-based dialysis fluid, while lipid-soluble drugs tend to remain in the blood.

3. Plasma Protein Binding

Only unbound drug molecules are able to pass through the pores in the semipermeable membrane.

4. Volume of Distribution

Compounds with small volumes of distribution (<1 L/kg, such as the aminoglycoside antibiotics and theophylline) usually demonstrate high dialysis clearance rates. Drugs with moderate volumes of distribution (1–2 L/kg) have intermediate dialysis clearance values, while agents with large volumes of distribution (>2 L/kg, such as digoxin and tricyclic antidepressants) have poor dialysis characteristics.

Hemodialysis

During hemodialysis, blood is pumped out of the patient at the rate of 300–400 mL/min and through one side of the semipermeable membrane of the artificial kidney by the hemodialysis machine. Dialysis fluid is pumped through the artificial kidney at a rate of 400–600 mL/min on the other side of the semipermeable membrane.

Computation of Initial Doses and Modification of Doses Using Drug Serum Concentrations

The calculation of initial doses and replacement doses for a drug that is significantly cleared by hemodialysis requires the knowledge of the PK parameters of the drug before dialysis and during dialysis.

For example, a patient is a 62-year-old, 5-ft 8-in male who weighs 65 kg, has chronic renal failure, and receives hemodialysis three times weekly (3 h in each session). Calculate loading dose that gives peak concentrations of 6–7 mg/L and replacement dose for tobramycin during the dialysis sessions. The patient is expected to have hemodialysis two-days after having the loading dose.

From population PK studies, the V_D of aminoglycosides is 0.26 L/kg.

The loading dose required to achieve peak plasma concentration of 6 mg/L is

$LD = C \cdot V_D$

$LD = 6 \times (0.26 \times 65) = 101$ mg (rounded to 100 mg).

After receiving this loading dose, tobramycin plasma concentration is expected to reach plasma level of 6 mg/L.

Before dialysis, tobramycin concentration is eleminated by the patient's own mechanisms. To note, the patient is in a case of renal failure which means that CrCl is zero. Therefore, the elimination rate constant (k) in this case is calculated as follow:

k (in h^{-1}) = 0.00293 · CrCl + 0.014

k (in h^{-1}) = 0.00293 x 0 + 0.014 = 0.014 h^{-1}

In the above example the patient receives hemodialysis three times weekly. We need to calculate plasma concentration just before hemodialysis (i.e. calculation of the decline in concentration from the time of administration of loading dose to the time of hemodialysis).
The above patient has received the loading dose two days (48 h) before hemodialysis.

$$C = C_0 . e^{-kt}$$

$$C = 6 . e^{-0.014 \, x \, 48} = 3.06 \text{ mg/L}$$

While the patient is receiving hemodialysis, tobramycin is eliminated by the patient's own mechanisms plus dialysis clearance. During hemodialysis, the average half-life for **aminoglycosides is 4 hours.**

$$k = \frac{0.693}{t_{1/2}} = 0.1732 \ h^{-1}$$

Dialysis session is 3 h, therefore

$$C = C_0 . e^{-kt}$$

$$C = 3.06 . e^{-0.173 \, x \, 3} = 1.82 \text{ mg/L}$$

After the dialysis, a postdialysis replacement dose could be given to increase the maximum concentration to its original value of 6 mg/L.

Replacement dose = (C_{max} – $C_{baseline}$) x V_D

Replacement dose = (6 – 1.82) x (0.26 x 65) = 70.6 mg (rounded to 70 mg).
For the calculation of the decline in plasma concentration of tobramycin during the time until the second hemodialysis session, keep in mind that K = **0.014 h^{-1}** as elemination is by the patient's own mechanisms only.

Peritoneal Dialysis

Peritoneal dialysis involves the surgical insertion of a catheter in the lower abdomen into the peritoneal cavity. The peritoneal membrane covering the internal organs is highly vascularized, so when dialysis fluid (1–3 L) is introduced into the peritoneal cavity using the catheter, waste products move from the blood vessels of the peritoneal membrane (a semipermeable membrane) into the dialysis fluid along a concentration gradient. The dialysis fluid is periodically removed from the peritoneal cavity and discarded.
Compared to hemodialysis, peritoneal dialysis removes drug much less efficiently. So, it is less likely that replacement drug doses will need to be given during intermittent peritoneal dialysis.

Obesity

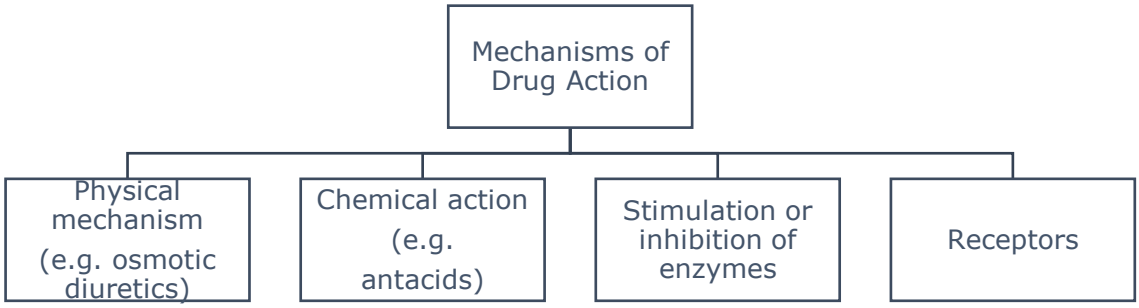
The presence of excessive adipose tissue can alter the pharmacokinetics of drugs by changing the volume of distribution.
Medications that have high lipid solubility tend to partition into adipose tissue, and the volume of distribution in obese patients for these drugs can be larger than in normal weight patients such as in the case of diazepam, carbamazepine, and trazodone.
Hydrophilic drugs tend to not distribute into adipose tissue so that the volume of distribution for many water-soluble drugs is not significantly different in obese and normal weight patients.

In addition to adipose cells, there are additional supportive tissues, extracellular fluid, and blood present in adipose tissue. For hydrophilic drugs with small volumes of distribution like aminoglycosides, the addition of just a few liters of extracellular fluid can alter the pharmacokinetics of these antibiotics and cases larger volume of distribution in overweight patients. For drugs with large and intermediate V_D, the effect of extra volume is not significant.

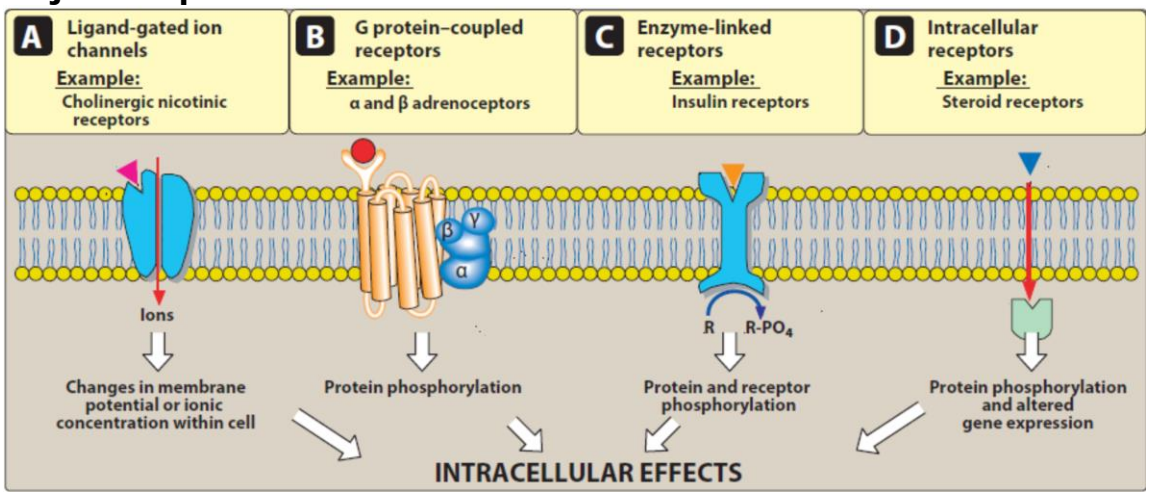
Another change that is found in obese individuals is increased glomerular filtration rates. This alteration affects hydrophilic drug compounds that are renally eliminated and will increase the renal clearance of the agent such as vancomycin, aminoglycosides, and cimetidine.

Obesity has variable effects on the metabolism of drugs. Hepatic clearance increases as with diazepam or decreases as with methylprednisolone.

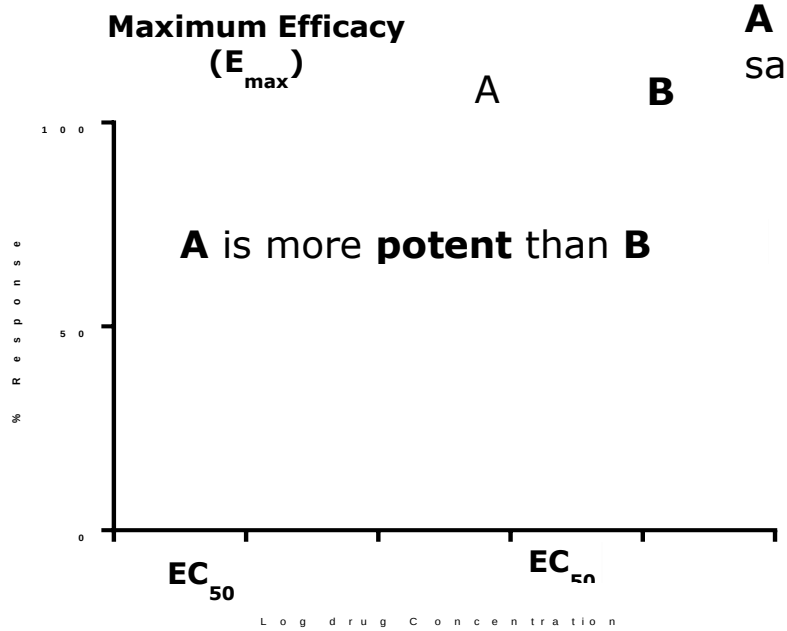
Basic Pharmacodynamics



Major receptor families



GRADED DOSE–RESPONSE RELATIONS

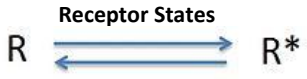


A and **B** have the same **Efficacy**

A is more **potent** than **B**

Intrinsic Activity

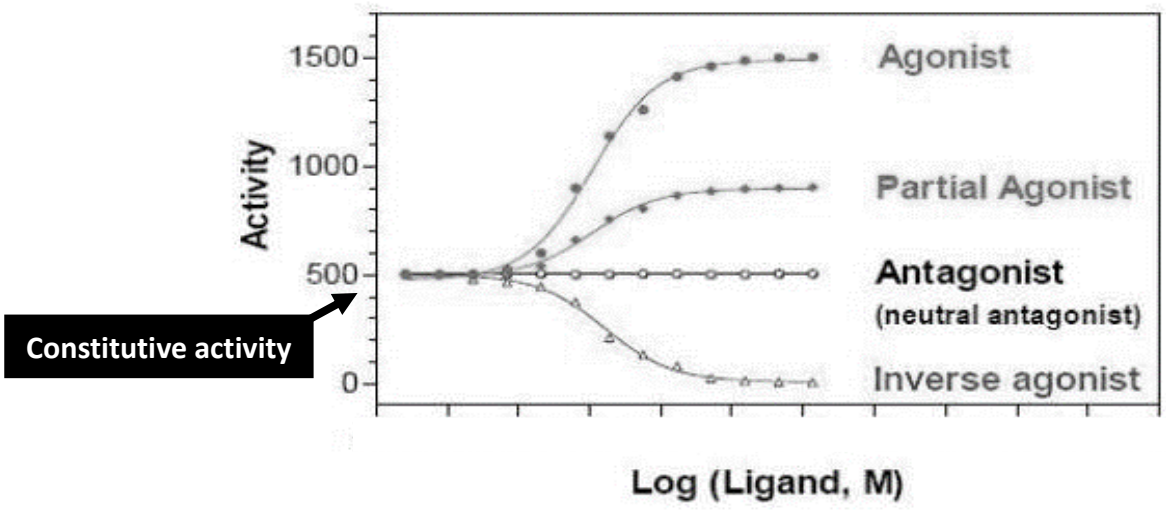
The intrinsic activity of a drug determines its ability to fully or partially activate the receptors.



Full agonist: drug binds to a receptor and produces a maximal biologic response. It stabilizes the receptor in its active state and is said to have an intrinsic activity of one.

Partial agonist: a drug binds to a receptor and does not produce a maximal biological response. It said to have an intrinsic activity > zero and < one.

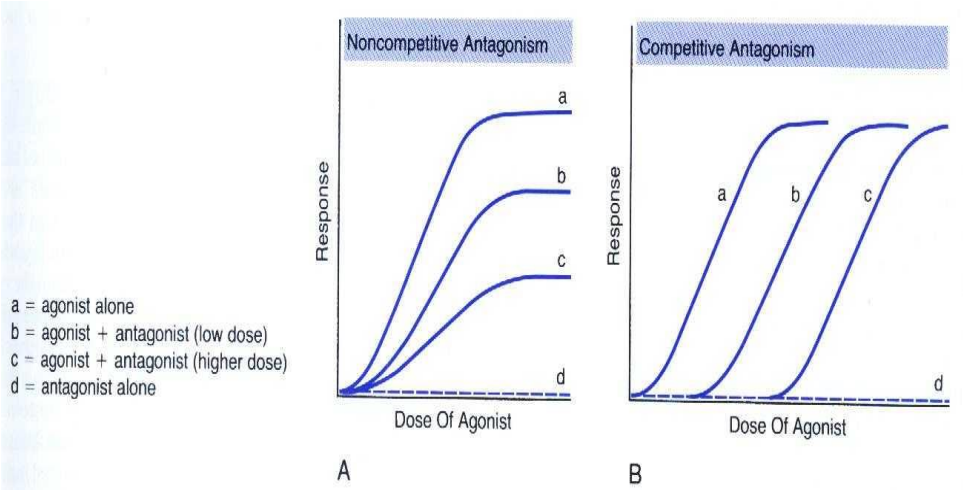
Inverse agonist: bind to receptor and reduce the effect. intrinsic activity less than zero



Types of Antagonists

1. **Pharmacologic Antagonists**

- **Competitive antagonists:** The competitive antagonist prevents an agonist from binding to its receptor.
- **Irreversible antagonists:** Irreversible antagonists bind covalently to the active site of the receptor, thereby reducing the number of receptors available to the agonist.
- **Allosteric antagonists:** This type of antagonist binds to a site ("allosteric site") other than the agonist-binding site and prevents the receptor from being activated by the agonist.



re 6–6. Dose-response curves in the presence of competitive and noncompetitive antagonists.

2. Physiologic antagonists

The antagonist is a different agonist that acts on the same tissue as the agonist, but combine with different receptors (from those of the agonist) to produce effects on the tissue that are opposite to those of the agonist.

Adrenaline antagonises the effect of endogenous histamine on blood vessels and bronchial smooth muscle when used in the treatment of anaphylactic shock.

3. Chemical Antagonists

A chemical antagonist interacts directly with the drug being antagonized to remove it or to prevent it from binding to its target

Examples; Dimercaprol, a chelator of lead and some other toxic metals, and pralidoxime, which combines avidly with the phosphorus in organophosphate cholinesterase inhibitors.

QUANTAL DOSE–RESPONSE RELATIONSHIPS

- Quantal dose–response curves are useful for determining doses to which most of the population responds.