**Lecture 1**

**LADME**
- what does the body do to the drug?  
  = Pharmacokinetics

**Pharmacodynamics**
- what does the drug do to the body  
  ~ Pharmacological effects  
  ~ Physiological effects

---

**Pharmacokinetics in your life**

A young child given an IM injection might ask: "How will that 'ouch' get from there to my sore throat?"

- The answer to this question is the basis of pharmacokinetics, i.e., how drugs move around the body and how quickly this movement occurs.
- During this semester many of the processes which control the absorption, distribution, metabolism, and excretion of drugs will be discussed.

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**What happens to a drug after its administration?**

1. Liberation = releasing
2. Absorption
3. Distribution
4. Metabolism
5. Excretion

---

**Disposition of drug in the body**

**Getting drug from one site to another**

- Oral Ingestion  
  - Drug  
  - Drug plasma protein complex  
  - Drug - tissue binding  
  - Drug - tissue elimination  
  - Metabolisation  
  - Drug and metabolites in urine  
  - Drug and metabolites in stool  
  - Drug and metabolites in expired air  

- Drug in GI Tract  
  - Drug absorption  
  - Drug A absorbtion  
  - Drug in plasma proteins  
  - Drug binds to plasma proteins  
  - Drug bound to receptor sites in tissue  
  - Drug elimination in tissue  
  - Drug in drug elimination  
  - Drug and metabolites in urine  
  - Drug and metabolites in stool  
  - Drug and metabolites in expired air
One, two, and three compartment models

Many of the processes involved in drug movement around the body are NOT saturated at normal therapeutic dose levels, making plasma concentration vs. time much simplified.

Two compartment model often has wider application.

Parameters to be measured in 2 compartment model:

1. Rate for absorption
2. DRUG IN CENTRAL COMPARTMENT
3. DRUG IN PERIPHERAL COMPARTMENT
4. DRUG ELIMINATED

Common parameters of a blood time curve:

- Peak Concentration
- Area under the Curve (AUC)
- Time of Peak

Therapeutic Range (window, index):

- All drugs are poisons
- Only proper administration determines whether a compound is beneficial or not
- The amount of drug administered and the resulting concentration in the body determines whether a drug is beneficial or detrimental
- The ideal range of drug concentrations within the body is referred as Therapeutic range (TR) or therapeutic window or therapeutic index (TI)
**Therapeutic Range of a drug in Plasma**

$TI = \frac{TD_{50}}{ED_{50}}$. So, the larger the TI the ??

**Drug concentration vs. Drug effect**

**Drug entered ~ Drug leaved**

Dose (absorbed) must match the rate the drug is metabolized + eliminated

![Drug concentration graph](image)

The goal of drug therapy: to maintain drug concentration in the TR

**Components of therapeutic administration**

- **Dose**: Amount of drugs administered at one time
- **Dosage (dosing) Interval**: Time between administration of separate drug doses
- **Route of administration**: Means by which the drug is given

**Plasma concentrations achieved can be controlled by the rate of drug absorption**

- Absorption too fast, resulting in dosing interval??

**Dose**

- **Unit**: mass (tablet, capsule, mL), mass/body weight (mg/kg, mg/lb (mg/mL))
- **Loading Dose**: A dose to quickly raise drug conc to therapeutic range. Used in critical condition: ex. life threatening infections, shock
- **Maintenance dose**: Dose required to maintain therapeutic concentration established by loading dose
Dosage Interval

What is the difference ??

A. 300 mg s.i.d.  
Vs.  
B. 100 mg t.i.d

Total Daily dose:

Patient compliance:

Therapeutic effect:

Possible toxicity

Route of administration

✓ Parenteral: beside the intestine  
✓ Intra arterial (IA)  
✓ Intra vascular (IV)  
✓ IV Bolus= single large volume  
✓ IV Infusion= slowly dripped over sec, min or hr

IV Bolus vs. IV infusion

IV Bolus  
- More concentration at intestinal tissue  
- Contact intestinal lining

IV Infusion  
- Less concentration at intestinal tissue

Think about it!

The difference between IA vs. IV?  
- Which one is more predictable in distribution?  
- Which one is more likely to cause (local) tissue toxicity?  
- Which one is more quickly to effect?  
- Which one would have higher plasma concentration?

Hint:

Route of administration - Parenteral

Subcutaneous (SC), Intramuscular (IM) and Intravenous (IV)  
- for drugs that are poorly absorbed form the GI tract  
- for agents that are unstable in the GI tract  
- ensure active drug absorption  
- more rapid/predictable than oral administration

Routes of choice for uncooperative or unconscious patients
Route of administration - Enteral

- Oral
  - Most pharmaceutical companies aim for this – it’s the most convenient and most economical
  - Factors that determine drug effect following oral absorption:
    - Rate & absorption extent by GI tract
    - Absorption site (=mainly small intestine, larger surface area)
    - Drug ionization state: non-ionized (lipid-soluble) forms are more favorably absorbed
    - First-Pass Effect
      - Drugs absorbed from the GI tract pass through the portal venous system to the liver, resulting in low systemic circulation due to extensive hepatic metabolism

- Rectal
  - Strategic placement: placement low in rectum, where veins drain into systemic circulation without passing through the liver, thus first pass metabolism by the liver can thus be bypassed

- Sublingual
  - Placement under the tongue allows some drugs to diffuse into the capillary network and therefore to enter the systemic circulation directly, enabling the drug to bypass the liver and avoid inactivation by hepatic metabolism.

Route of administration - Others

- Transdermal
  - Allows sustained, therapeutic plasma levels
  - Avoids first pass effect
  - Simple and high patient compliance

- Nasal
  - Route for peptides (degraded by gastric pH if taken orally) and to avoid first pass metabolism

- Inhalation
  - Choice for anesthetic agents and bronchodilators. (allows for high drug concentrations locally, not systemically)

- Conjunctival and intrathecal
  - Eye drops and injection into the subarachnoid space via a lumbar puncture needle.

How can drugs be administered

<table>
<thead>
<tr>
<th>Form</th>
<th>Skin or Mucosa</th>
<th>Example of Drugs Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral, parenteral</td>
<td>Oral tract, gastrointestinal tract</td>
<td>a. subcutaneous (local) b. intramuscular (local)</td>
</tr>
<tr>
<td>Topical, nasal</td>
<td>Nose, ear, conjunctival mucosa</td>
<td>a. eye drops (local) b. eye drops (ocular)</td>
</tr>
<tr>
<td>Nasal</td>
<td>Nose, ear</td>
<td>a. eye drops (ocular)</td>
</tr>
<tr>
<td>Intranasal</td>
<td>Bronchial, mucous, lung</td>
<td>a. respiratory spray (local) b. inhalation aerosol (systemic)</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>Skin</td>
<td>a. ophthalmic spray (local)</td>
</tr>
<tr>
<td>Intradermal</td>
<td>Skin</td>
<td>a. transdermal patch (local)</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Skin</td>
<td>a. transdermal patch (systemic)</td>
</tr>
</tbody>
</table>

How can drugs be administered

<table>
<thead>
<tr>
<th>Form</th>
<th>Skin or Mucosa-continued</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>a. vasopressor (nasal) b. peptide nasal spray (systemic)</td>
</tr>
<tr>
<td>Conjunctival</td>
<td>a. eye drops (ocular)</td>
</tr>
<tr>
<td>Nasal</td>
<td>a. eye drops (ocular)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>a. aerosol spray (local) b. inhalation aerosol (systemic)</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>a. ophthalmic solution (ocular)</td>
</tr>
<tr>
<td>Intradermal</td>
<td>a. transdermal patch (systemic)</td>
</tr>
</tbody>
</table>
### Common routes of drug administration

<table>
<thead>
<tr>
<th>Route</th>
<th>Bioavailability</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral (PO)</td>
<td>Good absorption</td>
<td>Absorption delayed.</td>
<td>No &quot;first pass&quot; effects.</td>
</tr>
<tr>
<td>Rectal (RE)</td>
<td>Good absorption</td>
<td>May allow use of high dose products.</td>
<td>May cause local irritation.</td>
</tr>
<tr>
<td>Intramuscular (IM)</td>
<td>High absorption</td>
<td>Faster absorption and higher plasma concentration.</td>
<td>Muscle pain, bruising, infection.</td>
</tr>
<tr>
<td>Intravenous (IV)</td>
<td>100% absorption</td>
<td>Complete and rapid absorption.</td>
<td>None</td>
</tr>
<tr>
<td>Subcutaneous (SC)</td>
<td>Moderate</td>
<td>Lower risk of adverse effects.</td>
<td>Volatility in absorption rates.</td>
</tr>
</tbody>
</table>

**Effect of administration routes**

Administration route affects speed and extent of absorption.

- **Faster absorption and higher plasma concentration by IM vs SC**

**Movement of Drugs**

"How does the medicine know where to go?"

Drug distribution is directed by the physicochemical properties of the drug and the physiology of the body membranes and fluids.
Absorption mechanisms - passive diffusion

Prerequisite: Drug has to be in solution

- Passive diffusion
  - Facilitate transport
  - Active transport
  - Convective transport
  - Ion-pair transport
  - Pinocytosis (exception)

Spontaneous movement of solutes from high to low concentration follows: Fick’s Law of Diffusion

Fick’s Law of Diffusion

To describe the passive flux of molecules down a concentration gradient:

\[
\frac{dc}{dt} = \frac{D \cdot c_0}{t} \cdot \frac{c_1}{t}
\]

Diffusion rate \( \propto \) drug concentration

Factors affecting the Passive diffusion:
- A lipid:aqueous drug partition coefficient
- The ionization state
- The pH and the drug pKa (determining the drug’s ionization state)

Facilitated transport (diffusion)

Similar to Active transport:
- Carrier mediated
- Can be competitive
- Can be saturable

Does Not need energy, work with conc. gradient

Passive diffusion vs. Facilitated diffusion

1. Does Not need energy.
2. Work with conc. gradient

1. Does Not need energy.
2. Work with conc. Gradient
3. Carrier mediated
4. Saturable
**Absorption mechanisms**

**Active transport**
- Against concentration gradient, do not stop at equilibrium, cause intracellular accumulation
- Examples: Na, K, Amino acids, Vitamins, Sugars, Hormones, Larger drugs
- Against concentration gradient:
  - Needs energy (ATP)
  - Can be competitive
  - May be saturable

**Active transport vs Diffusion**
- Rate of Absorption
- Active transport: may be saturable
  - Depending on transporting carrier or enzyme
- Diffusion: not so important for drugs (∵ size restriction)

**Convective transport**
- Absorption through pores (7-10 Å), for MW up to 400
- Both ions and neutral molecules can pass, depending on size
  - Diffusion controlled, driven by concentration gradient
  - Not so important for drugs (size restriction)

**Summary – factors affecting drug movement**
- A. Charge (= polarity = affected by environmental pH)
- B. Lipophilicity (fat loving)
- C. Concentration gradient
- D. Molecular size
- E. Temperature of cellular environment
- F. Thickness of membrane
  - Small, lipophilic drug with high concentration gradient, moves the best
**Drug absorption**

Absorption: Uptake of a drug into the systemic circulation from site of administration to systemic circulation (blood stream)

- Break into smaller pieces
- From solid to solution

Drugs in liquid dose form do not have a dissolution step thus are more readily absorbed than solid dosage form

**How well drug absorbed is expressed by Bioavailability (F)**

\[ F = \frac{\text{Amount of drug in Plasma}}{\text{Dose}} = \frac{\text{AUC oral}}{\text{AUC i.v.}} \]

(Ranges from 0 – 1)

**Factors affecting bioavailability**

- Dissolution of drug
- Drug form or formulation (salt, ester etc.)
- Dosage form (tablet, capsule)
- Route of administration
- GI tract
  - pH (ionization of drug)
  - Metabolism (first pass effect)
- Bacteria
- Stay time (emptying time)
- Food content

**Dissolution of drugs on absorption**

Taking medicine with more water increases drug absorption

The rate of absorption may be the same but the extent of absorption may be different

**Effect of drug formulations**

Pro-drugs = drugs that need to be metabolized before desired action is available

- Dexamethasone: can be prepared in two derivatives
  - Sodium hemisuccinate-Ester hydrolyze slower than Phosphate-Ester
  - For longer duration = For faster availability

**A = Drug absorption**
Effect of drug formulations

Phosphate hydrolyzed faster and better so higher plasma concentration is reached.

Sulfobenzoate hydrolyzed slower so longer duration is expected.

Effect of dosage forms

Serum concentration of dipyridamole (anti-coagulant) in 5 experimental subjects.

Whole tablet of dipyridamole
- Lower peak concentration
- And variable rate of absorption

Crushed tablet of dipyridamole
- Higher peak concentration and faster absorption

Effect of administration route

IV > SL > IM ≥ SC ≥ PO ≥ TP

Instant - sec - min - hr - --- hr

Lipophilicity vs. hydrophilicity

Hydrophilic drugs:
- Better absorbed through IM, SC
  (∵ administered in intercellular space)

Lipophilic drugs:
- Better absorbed through intestine
  (∵ tight cellular junctions)

Applications:

Sustained release:
- Intestinal therapy

Regular vs. Sustained Release

«lower steady state concentration & longer duration
Lower overall bioavailability

Think about it!

IV bolus vs. IV infusion in digoxin

- Positive inotropic agent by inhibiting Na-K-ATP pump thus providing more Ca available for cardiac muscle contraction
- Low Therapeutic Index
- Side effects including anorexia, vomiting, diarrhea, and arrhythmias

IV bolus or IV infusion? Why?
**Effect of pH and ionization**

Many drugs are acids or bases. Only the non-ionized form can cross the membrane by passive diffusion.

**Effect of pH on Ionization**

Effect of pH on Ionization

**Commonly used pKa values**

<table>
<thead>
<tr>
<th>Drug</th>
<th>pKa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>9.8</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>8.4</td>
</tr>
<tr>
<td>Propranolol</td>
<td>9.5</td>
</tr>
<tr>
<td>Thiopental</td>
<td>7.5</td>
</tr>
<tr>
<td>Dopamine</td>
<td>9.0</td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>6.8</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>8.5</td>
</tr>
<tr>
<td>Sulmethoxazole</td>
<td>5.5</td>
</tr>
<tr>
<td>Morphine</td>
<td>8.6</td>
</tr>
<tr>
<td>Warfarin</td>
<td>5.0</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>9.5</td>
</tr>
<tr>
<td>Penicillins</td>
<td>2.8</td>
</tr>
</tbody>
</table>

**Henderson and Hasselbalch Equation**

Describes the relationship between pH and pKa for:

- **Weak Acid:** \[ AH \rightleftharpoons A^- + H^+ \]
- **Weak Base:** \[ BH^+ \rightleftharpoons B + H^+ \]

\[
\text{pH} - \text{p}K_a = \log_{10} \frac{[\text{A}^-]}{[\text{AH}]} = \log_{10} \frac{[B]}{[\text{BH}^+]} = -\frac{\text{pH} - \text{p}K_a}{10}
\]
Ion trapping of acidic drugs

Ion trapping of basic drugs

Ion trapping of salicylate

By definition:

Henderson and Hasselbalch Equation:

\[ \text{pH} = \text{pK}_a + \log \left( \frac{[A^-]}{[HA]} \right) \]

Ex. At pH 8.4 in urine: 8.4 - 7.4 = 1.0 = \log_{10} \left( \frac{[A^-]}{[HA]} \right)

\[ \frac{[A^-]}{[HA]} = 10^{1.0} = 10 \]

~90 % Phenobarbital is “trapped” in this urine

Ex. At pH 8.4 in plasma: 7.4 - 8.4 = -1.0 = \log_{10} \left( \frac{[A^-]}{[HA]} \right)

\[ \frac{[A^-]}{[HA]} = 10^{-1.0} = 0.1 \]

~90 % Quinine is “trapped” in the plasma

Acid (salicylate) \pKa = 4.4
Stomach contents \pH = 2.4
Plasma \pH = 7.4

See examples below

Acidic drug is more ionized in alkaline environment
Basic drug is more ionized in acidic environment

A weak base is well absorbed in the stomach.
For quinine
Basic drug (quinine) \pKa = 8.4
Stomach \pH = 2.4
Plasma \pH = 7.4

See examples below

A weak base is not well absorbed from the stomach.
Basic drug is better absorbed in alkaline environment
**Ionization of Quinine in different pHs**

<table>
<thead>
<tr>
<th>pH - pK_a</th>
<th>BH^+ concentration</th>
<th>B concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH_1 = 4.4</td>
<td>10^3 = 1,000</td>
<td>1</td>
</tr>
<tr>
<td>pH_2 = 6.4</td>
<td>10^2 = 100</td>
<td>1</td>
</tr>
<tr>
<td>pH_3 = 8.4</td>
<td>10^0 = 1</td>
<td>1</td>
</tr>
</tbody>
</table>

**Ion trapping of Aspirin in the stomach**

1. Acidic drug in acidic Environment, thus non-ionized and readily across the lumen
2. Once in the cell, intracellular environment becomes alkaline, thus ionize the drug and "trap" the drug within the cell

**Is Ion trapping all bad?**

**Situation 1: Drug overdose**

**Situation 2: Drug has toxic metabolites eliminated by kidney**

**Factors affecting GI absorption**

**Factors affecting GI absorption**
- Surface area
- 1st pass effect
- Food interaction
- Degradation by GI enzyme or gastric acid
- Gastric emptying time (slow emptying delay resorption)

**Presystemic metabolism**

Drugs metabolized before entering the systemic circulation
- metabolism in gut wall
- terbutaline, salbutamol

**First pass effect**

After GI absorption, drugs enter liver (through portal vein) for metabolism before they could reach the site of action, therefore, the bio-availability of drugs is greatly reduced
First pass effect

40 mg oral dose of the drug gives rise to the same target organ concentration as delivered by 2 mg injection of the drug.

The first-pass effect of tranquilizer Diazepam is so extensive that little reach the blood. DO NOT recommend PO.

Degradation by enzyme and other factors

Effects of food on drug absorption

Legend:
Reduced = drugs whose absorption are reduced by food intake

Example of food delaying absorption

Whole tablet of dipyridamole
Crushed tablet of dipyridamole
Whole tablet 2 hr before lunch
Slow absorption with food & Un-disintegrate tablet give 2nd peak

Clinical Application
--why is Ep co-administered

Lidocaine:
- local anesthetics
- induce local numb

Epinephrine:
- α1 adrenergic agonist
- Vasoconstrictor
- ↑ blood pressure

Effects of food content on drug absorption

Griseofulvin

Effect of tissue perfusion on absorption
Lecture 3

**D = Drug distribution**

Most drugs are not beneficial unless they reach the target tissue.

- Imagine a cardiac drug can not reach the myocardium?
- Imagine a tranquilizer unable to reach the brain?

**Definition**

Movement of drug from the systemic circulation into tissue.

Reversible movement of drug between body compartments.

**Drug distribution**

Movement between central and peripheral compartments.

<table>
<thead>
<tr>
<th>Central Compartment</th>
<th>Examples of Peripheral Compartment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>Fat Tissue</td>
</tr>
<tr>
<td>Heart</td>
<td>Muscle Tissue</td>
</tr>
<tr>
<td>Kidney</td>
<td>Connective Tissue</td>
</tr>
<tr>
<td>Liver</td>
<td>Brain</td>
</tr>
<tr>
<td>Lungs</td>
<td>Adipose Tissue</td>
</tr>
</tbody>
</table>

For a 70 kg human, Total Body Water ~ 60% Body Weight:

- ~ 20% BW = Extracellular Fluid (45 L)
- ~ 40% BW = Intracellular Fluid (30 L)
- ~ 5% BW = Plasma Water (5 L)
- ~ 15% BW = Interstitial Fluid (10 L)

**Drug distribution pathway**

Barriers to Drug Distribution:

- Both hydrophilic and lipophilic free drugs can pass through fenestrations (windows, pores) in the capillary wall.
- Drugs bound to protein.

Blood perfusion rate:

- Higher
- Lower
Blood-Brain barrier has tight endothelial junctions (astrocyte, glial cells)

Only extremely lipophilic drugs can pass through BBB

Special barriers:
- Prostate: only selective antibiotics work
- Eye ball: need direct injection
- Placenta: a poor barrier to drugs

Drug distribution depends on how well tissue is perfused with blood

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Percent Body Weight</th>
<th>Percent Cardiac Output</th>
<th>Blood Flow (μl/min, p-lumen)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>86.4</td>
<td>1.6</td>
<td>500</td>
</tr>
<tr>
<td>Liver</td>
<td>7.6</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>Heart (muscle)</td>
<td>6.4</td>
<td>4</td>
<td>75</td>
</tr>
<tr>
<td>Skin</td>
<td>7.0</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Muscle (diaphrag)</td>
<td>66.0</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>7.0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

1. Thiopental = inductive anesthetic
2. Thiopental = very lipophilic, quickly pass BBB and distribution to the brain
3. Study distributions of drugs continue to distribute to other tissues, dropping blood concentration in the brain
4. Redistribution = drugs distribute to the brain (tissue), back to the blood, and then to a second tissue (e.g., fat)

Drug distribution depends on the extent of drug-protein binding

Only protein-free drug can pass membrane and is pharmacologically active can be metabolized and excreted

Drug-protein binding may be decreased by liver and protein-losing renal diseases

<table>
<thead>
<tr>
<th>LIVER DISEASES</th>
<th>RENAL DISEASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilantin</td>
<td>Creatinine</td>
</tr>
<tr>
<td>Dihydropyridines</td>
<td>Creatinine</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Creatinine</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>Creatinine</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Creatinine</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>Creatinine</td>
</tr>
<tr>
<td>Triamterene</td>
<td>Creatinine</td>
</tr>
</tbody>
</table>

Representative proteins to which drugs bind in plasma

<table>
<thead>
<tr>
<th>Protein</th>
<th>Molecular Weight</th>
<th>Normal Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>67,000</td>
<td>3.5-5.5</td>
</tr>
<tr>
<td>Total glycoproteins</td>
<td>54,000</td>
<td>0.4-6.0</td>
</tr>
<tr>
<td>Lipoproteins</td>
<td>200,000-2,000,000</td>
<td>Variable</td>
</tr>
<tr>
<td>Corinol binding</td>
<td>53,000</td>
<td>0.01-1.0</td>
</tr>
<tr>
<td>globulin (transcobalamin)</td>
<td>500</td>
<td>0.5-5.0</td>
</tr>
<tr>
<td>RBC</td>
<td></td>
<td>Mostly for acidic drugs binding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mostly for basic drugs binding</td>
</tr>
</tbody>
</table>
Calculation of drug-protein binding ($F_b$)

Equilibrium constant

$$K_a = \frac{[DP]}{[D][P]}$$

$$[DP] = K_a \times [D][P]$$

$$F_b = \frac{[DP]}{[D]_{total}} = 1 - F_u$$

$F_u$ can be experimentally measured w/o knowing protein concentration.
Ex. microdialysis

Protein binding data of some drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Unbound (100%)</th>
<th>Fraction unbound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aseredol, Lixipam</td>
<td>100</td>
<td>16</td>
</tr>
</tbody>
</table>
| Procainamide, Diphen 
| 50             | 2               |
| Diphenhydramine       | 20             | 0.5             |
| Quinidine             | 0.2            | 0.1             |
| Phenytoin, Phenytozide|
| Tizanidine            |

Drug-protein binding information can be very important for drugs with high protein binding (see below).

Protein binding is a competitive process, depending on (1) affinity (2) concentration

10 As bound to protein, B has higher affinity for protein.
B could displace A and $\uparrow$ [free A] doubles.

For a drug that is 99% protein-bound, 2% change in protein binding causes plasma drug concentration "Triples".

High protein-bound drugs require loading dose maintenace dose.

Replacement of high protein bound drugs can increase toxicity

<table>
<thead>
<tr>
<th>Drug displaced</th>
<th>By concomitant drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Ethinyl estradiol</td>
</tr>
<tr>
<td>Methysergide</td>
<td>Nifedipine calcium</td>
</tr>
<tr>
<td>Ophthalmazone</td>
<td>Pencyclidone</td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Sulindac</td>
<td>Sulindac</td>
</tr>
</tbody>
</table>

Use of aspirin, phenylbutazone, sulfa drugs, etc may potentiate the anticoagulant effect of warfarin and hypoglycemic effect of tobutamide.

Summary for drug-protein bindings

1. Occur in plasma & tissue
2. Primarily to albumin
3. Is reversible
4. By weak bonds (van der waal’s and ionic bonds)
5. Mostly unspecific to many drugs
6. Can have more than 1 binding sites
7. Can be displaced by drugs w/ higher affinity
8. Delays urinary excretion ($\therefore$ not filtered)
9. Increases biological half-life ($\therefore$ not filtered or metabolized)
10. Can be saturated

Volume of distribution ($V_d$)

$$V_d = \frac{Dose}{[Plasma drug]}$$

Ranges from 7 – 40000 L.

What does $V_d > 5L$ in a 70 kg man mean?
Volume of Distribution (Vd)

Assumptions:
1. Drug is equally distributed throughout the body
2. Blood concentration is equilibrium to tissue concentration

Apparent Volume of Distribution (Vd) is more accurately used because Vd is a mathematically derived value, not a real volume

Vd can be misleading:
- Ex. Digoxin is sequestered in the muscle and heart
- Vd can be different in different body composition:
  - Ex. a fat dog and lean dig with the same weight

Introduction to Drug Metabolism

Metabolism
A drug’s Fate in the body

Biotransformation is part of the metabolism process

M=Drug biotransformation

Biotransformation:
Definition: conversion of a drug into metabolites
Purpose: to increase hydrophilicity of the drug

Is classified as phase 1 and phase 2 pathways:
- phase 1: non-synthetic or functionalization reactions introduce or uncover a hydrophilic functional group
- phase 2: synthetic or conjugation reactions addition of an endogenous, water-soluble small molecules

M=Drug biotransformation

Include two major reaction phases:

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>What does it do?</td>
<td>Add functional group</td>
</tr>
<tr>
<td>Introduce/expose functional group</td>
<td>The purpose? To ↑ drug polarity for better excretion</td>
</tr>
</tbody>
</table>

Phase I & II does NOT always occur together
Phase I does NOT always precede phase II reactions

Major phase I & II reactions

Common drug biotransformation processes:

<table>
<thead>
<tr>
<th>Phase I Reactions</th>
<th>Phase II Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidation</td>
<td>Glucuronide conjugation</td>
</tr>
<tr>
<td>Aromatic hydroxylation</td>
<td>Ester glucuronide</td>
</tr>
<tr>
<td>Side chain hydroxylation</td>
<td>Amide glucuronide</td>
</tr>
<tr>
<td>N- &amp; O-sulfoxidation</td>
<td>Peptide conjugation</td>
</tr>
<tr>
<td>Deamination</td>
<td>Glutathione conjugation (GSH)</td>
</tr>
<tr>
<td>Sulfoxidation</td>
<td>Methylation</td>
</tr>
<tr>
<td>Sulfonation</td>
<td>Acetylation</td>
</tr>
<tr>
<td>Reduction</td>
<td>Sulfite conjugation</td>
</tr>
<tr>
<td>Hydration</td>
<td>Glutathione conjugation</td>
</tr>
<tr>
<td>Ester hydrolysis</td>
<td>Fatty acid conjugation</td>
</tr>
<tr>
<td>Amide hydrolysis</td>
<td>Glucuronide conjugation = addition of glucuronide</td>
</tr>
</tbody>
</table>
**Relationships of phase I & II reactions**

<table>
<thead>
<tr>
<th>Phase I Reaction</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidation</td>
<td>Phenacetin, acetaminophen, chloramphenicol, chlorpromazine, methadone, paracetamol, quinidine, teicoplanin, verapamil</td>
</tr>
<tr>
<td>Reduction</td>
<td>Acetaminophen, chloramphenicol, meperidine, nortriptyline, pethidine, propofol, teicoplanin, verapamil</td>
</tr>
</tbody>
</table>

Other drugs above undergo either phase 1 or phase 2 metabolisms.

**Introduction to metabolizing enzymes**

**Cytochrome P-450**

P-450 plays a central role in the metabolism of many xenobiotics, catalyzing both detoxification and bioactivation reactions.

P-450 can introduce hydroxyl groups (-OH) into structures as un-reactive as hydrocarbon chains and aromatic rings, initiating conjugation process.

Location of enzymes:
Liver >> intestine ~ lung ~ skin

**Biotransformation and activity**

Diseases could gain or lose their pharmacological activity after metabolism.

**Cyp 450 dependent-mixed-function oxidases (MFO)**

**Monoxygenase responsible for oxidation and reduction of drugs**

**Electron transfer system**

**Overall reaction:**

RH + O2 + NADPH + H+ → ROH + H2O + NADP+

**Side-chain hydroxylation of Pentobarbital**

Pentobarbital → Hydroxypentobarbital

**Active drug**

[Chemical structure of Pentobarbital and Hydroxypentobarbital]

**Inactive metabolite**

[Chemical structure of Pentobarbital and Hydroxypentobarbital]
**Deamination of Amphetamine**

Amphetamine $\rightarrow$ Phenylacetone  
\[ \text{Oxidative deamination} \]

Amphetamine (Active drug)  
Phenylacetone (Inactive metabolite)

**Demethylation of Codeine**

Codeine $\rightarrow$ Morphine  
\[ O\text{-dealkylation} \]

Codeine (Active drug)  
Morphine (Active metabolite)

**Phase II conjugation reactions**

**Mechanisms of conjugation**

1. To raise the energy level for preparation of conjugation reaction  
2. Use of an appropriate transferase to complete the connection

The most common conjugating agents are:

Conjugation Reaction | Conjugating Agent | Functional Group Combined With
--- | --- | ---
Glucuronidation | Glucuronic acid | OH, COOH, NH₂, SH
Sulfation | Sulfate | OH, COOH, NH₂, SH
Amine N-acetylation | Acetyl-CoA | NH₂
Amine N-methylation | S-adenosylmethionine | NH₂
Glutathione conjugation | Glutathione | Amine, amine oxides, aromatic or heterocyclic xenobiotics

The most seen functional groups for conjugation are: OH, COOH, NH₂, SH

**Biotransformation reaction by functional groups**

**CHEMICAL CLASS AND FUNCTIONAL GROUP OF DRUG**  
**TYPE AND SEQUENCE OF METABOLIC REACTION**

- **Aromatic carboxyl group**: Ring hydroxylation, amino acid or glucuronide conjugation
- **Aliphatic primary amines**: Deamination, methylation, N-acetylation, or glucuronide or sulfonate conjugation
- **Aromatic primary amines**: Ring hydroxylation, amino acid or glucuronide or sulfonate conjugation or methylation
- **Semi-aromatic amines**: Deamination, methylation, N-acetylation or glucuronide or sulfonate conjugation
- **Sulfonated group**: Glucuronide or sulfonic acid conjugation, aromatization or glucuronide or sulfonic acid conjugation

When you see the (left side) functional groups on a drug, it is likely to perform the (right side) conjugation reaction and sequences.

Examples refer to salicylic acid biotransformation in the next page.
Biotransformation of salicylic acid

Conjugations are not all good

Regulation of drug biotransformation

Metabolism of mephenytoin enantiomers
**Drug-Enzyme Interactions**

1. Enzyme competition
   - 2 drugs using the same enzyme
2. Enzyme inhibition
   - 1 drug ↓ the metabolism of the other drug
3. Enzyme induction
   - drug ↑ the metabolism of drug
   - 1. auto induction
     - drug ↑ self metabolism
   - 2. foreign induction
     - drug ↑ other drug's metabolism

Enzymes may ↑ when they are repeatedly exposed to the drug. Shortening the drug's effective time. Develop TOLERANCE (ex. Barbiturates, narcotics, alcohol)

**Competition of enzymes**

<table>
<thead>
<tr>
<th>Inhibitors</th>
<th>To be Inhibited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Anti uric acid synthesis anti-inflammatory</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Anti arthritic</td>
</tr>
<tr>
<td>Aminopyrine</td>
<td>Anti uric acid synthesis anti-cancer</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Anti arthritic</td>
</tr>
</tbody>
</table>

*Alcohol dehydrogenase inhibitor* ↑ alcohol accumulation

Quick absorption, slow excretion. Ideal for treating alcoholism

<table>
<thead>
<tr>
<th>Inhibitors</th>
<th>To be Inhibited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celebrex</td>
<td>Anti inflammatory</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Anti inflammatory</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Anti inflammatory</td>
</tr>
</tbody>
</table>

**Regulation of drug biotransformation**

**Enzyme induction**

<table>
<thead>
<tr>
<th>DRUGS CAUSING AUTO-INDUCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Penicillin</td>
</tr>
<tr>
<td>Tolbutamide</td>
</tr>
</tbody>
</table>

**Enzyme inhibition**

<table>
<thead>
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<td>Warfarin</td>
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<td>Naproxen</td>
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**Regulation of drug biotransformation**

**Foreign inductions**

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<td>Anti inflammatory</td>
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<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Inhibitors**

<table>
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<td>Alcohol</td>
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**Metabolism**

**Foreign induction**

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**Regulation of drug biotransformation**

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**Metabolism**

**Foreign induction**

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</tr>
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<td>Naproxen</td>
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</tr>
</tbody>
</table>
Example: Induction of cytochrome P-450

**Table 14.3: Mechanisms of Induction of Cytochrome P-450 Enzymes**

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Typical Inducer</th>
<th>Mechanism of Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A1</td>
<td>Phenobarbital</td>
<td>Transcriptional activation</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>3-Methylcholanthrene</td>
<td>Transcriptional activation</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Meclofenamate</td>
<td>Transcriptional activation</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Carbamazepine</td>
<td>Transcriptional activation</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>Ethanol, acetone</td>
<td>Transcriptional activation</td>
</tr>
</tbody>
</table>

**Commonly used**

In exposure to certain xenobiotics, P-450 ability to metabolize drugs could result in higher plasma concentration and toxicity. Drug-drug interaction is complicated in cases where one drug competes with another for the same enzyme. Mechanisms proposed for P-450 inhibition include:

1. Competitive inhibition
   - Two drugs (substrates) compete for the same enzyme.
   - The real drug binding and metabolism are blocked.

2. Non-competitive inhibition
   - Production of metabolites with higher affinity to P-450 than Parent drug.
   - Produces highly reactive metabolites that bind to P-450 and destroys P-450 (suicide substrate).

So drugs gradually lose their effectiveness.

**Example: Induction of (phenacetin) metabolism**

Phenacetin is readily de-alkylated to acetaminophen.

**Table 14.6: Effect of a Diet Containing Charcoal-Brained Beef on the Plasma Concentration of Phenacetin in Rats**

<table>
<thead>
<tr>
<th>Diet</th>
<th>CYP 1A1 &amp; 1A2</th>
<th>Phenacetin Level (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>12.0 (1)</td>
<td>925 (2)</td>
</tr>
<tr>
<td>Charcoal beef</td>
<td>210 (3)</td>
<td>425 (2)</td>
</tr>
</tbody>
</table>

People who took phenacetin and charcoal beef have significantly lower plasma phenacetin, this is a typical example of CYP 1A1 & 1A2 induction.

Other common dietary factors which are also P-450 inducers include cigarette (1A, 3A), coffee (1A, 2E) and alcohol (2E). Wonder why you are tolerant to caffeine or alcohol? Some vegetables like cabbage, cauliflowers and asparagus are P-450 inactivators (1A, 2E). Wonder why they are anti-cancerous?

**Inhibition of Cytochrome P-450**

Exposure to certain xenobiotics decreased P-450 ability to metabolize drugs:

- Inhibition could result in higher plasma concentration and toxicity.
- Drug-drug interaction complicated this situation where one drug can compete with another for the same enzyme.
- 4 mechanisms are proposed for P-450 inhibition:
  1. Competitive inhibition
  2. Non-competitive inhibition
     - Production of metabolites with higher affinity to P-450 than parent drug.
     - Produces highly reactive metabolites that bind to P-450 and destroys P-450 (suicide substrate).

**Example: Enzyme inhibition Naringenin and Bergamottin**

- Grapefruit can have a number of interactions with drugs, often increasing the effective potency of compounds. Grapefruit contains naringenin and bergamottin, which inhibit the cytochrome P450 isoenzyme CYP3A4 in the liver. It is via inhibition of this enzyme that grapefruit increases the effects of simvastatin, terfenadine, felodipine, nifedipine, verapamil, estradiol, midazolam, and cyclosporine A.
- Grapefruit seed extract is a strong antimicrobial with proven activity against bacteria and fungi. It also has antioxidant properties and low glycemic index.
- Away with grapefruit products while taking medicines.

**Summary**

Regulation of drug biotransformation:

1. Genetic polymorphism
2. Enzyme inhibition
3. Enzyme auto induction
4. Enzyme foreign induction
5. Enzyme competition
6. Stereo-specific metabolism

Unwanted drug toxicity → Treatment Failure

**Cats are not Little Dogs**

Species differences in biotransformation:

- A drug that’s safe in one species may produce severe side effects in another.
- Less glucuronic acid conjugation in cats.
  - Aspirin
  - Acetaminophen
    - Liver failure, hemolysis, heinz body, methemoglobin

Detoxification of acetaminophen

1 = major pathway
3 = intoxication pathway
4 = detoxification pathway

(N-acetyl-papr-benzoquinone imine)

Malnutrition and alcohol (barbituate) ↑ susceptibility to Tylenol toxicities

Supplement of N-acetylcysteine keep this pathway going

Detoxification pathways of acetaminophen

E = Drug excretion
movement of drug out of the body

Drug excretion pathways

Renal

Glomerular filtration
125 ml/min (inulin)
625 ml/min ex. P-aminohippurate, penicillin

Tubular secretion

Hepatic

Tubular secretion

Biliary

Intestinal

Nephron

Drug excretion - Renal

Mechanism for renal excretion:

Renal

Tubular reabsorption

Glomerular filtration

Tubular secretion

Active or passive pH-dependent process
For MW<500, Capacity limited (saturable)
Most drugs has small MW, water soluble conjugates

Drug excretion - Renal Nephron

Lecture 5
Renal regulations of low MW molecules

1. Most molecules are resorbed by concentration gradient
2. Angiotensin II stimulates resorption of Na, Cl, & H2O
3. Na-K-2Cl co-transporter
4. Na-Cl co-transporter
5. Aldosterone ↑ Na resorption by open Na channel, Na-CI co-transporter
ADH stimulates it
Furosemide blocks it
Thiazides block it

Factors affect renal excretion of Drug

1. Acid system
   - ex. penicillin, probenecid
   - Amino acids
   - p-Aminophenolic acid
   - Aminosalicylate
   - Dihydromorphine
   - Penicillin
   - Metformin

2. Base system
   - ex. ranitidine
   - Histidine
   - Mepiperpenal
   - Methylisonicotinate

Drug excretion - Renal

Tubular re-absorption: passive or active transport (glucose)

H2O re-absorption = 1.5L/day
Reabsorption is pH dependent:
more ionized = less absorption

Drug excretion - enterohepatic

Liver-bile-intestine pathways
For molecules with strong polar groups
Such as Conjugates
Mostly for larger molecules (MW > 500)
Enterohepatic circulation
Drug can be secreted into the bile
→ to the intestine
→ hydrolyzed in the intestine
→ re-absorbed to liver for systemic availability
A reverse of conjugation elimination procedure

Drug excretion - enterohepatic & biliary excretion

Enterohepatic Circulation
Cortisol
Dihydroepiandrosterone
Estradiol
Estrone
Estradiol
Ethionamide
Ethamibutol
Ethylmorphine
Dexamethasone
Diazepam
Diazoxide
Diazoxide
Diazoxide

Biliary Excretion (intact or as metabolites)
Cefametile
Diazepam
Estradiol
Ethionamide
Ethamibutol
Estradiol
Ethionamide
Ethamibutol
Estradiol
Ethionamide
Ethamibutol

Drugs possibly through enterohepatic & biliary excretion

Cortisol
Dihydroepiandrosterone
Estradiol
Estrone
Estradiol
Ethionamide
Ethamibutol
Ethylmorphine
Dexamethasone
Diazepam
Diazoxide
Diazoxide
Diazoxide
**Extraction Ratio (ER)**

- Represents the magnitude of the first pass hepatic effect
- A drug with a high ER exhibits high extraction by the liver.
- High ER drugs may show higher variations in interpatient bioavailability than low ER drugs.

High ER = fast metabolized by the liver

Extraction ratio = \( \frac{C_{in} - C_{out}}{C_{in}} \)

---

**Other excretion pathways**

- Most drug in blood will be detectable in Milk
- Pulmonary
- Skin
- Salivary

Volatile substances
- Ethanol-drush
- Paraldehyde-anesthetics

A minor pathway
- Passive diffusion
- Vitamin B

pH 6.4-7.6
- Passive diffusion ex. Sulfonamides

pH 6.5 (5.5-8.4)
- for lipid soluble, non-ionized
  Salivary = free plasma level prednisolone glucocorticoids

---

**Drugs by hepatic excretion**

Flow limited:
- excretion of high extraction drug is limited by blood flow

Capacity limited:
- excretion of low extraction drug is limited by enzyme capacity

---

**How fast drug excreted can be expressed by clearance**

**Clearance (CL)**

Units = volume/time = ex. L/day

Clearance can be thought of as the intrinsic ability of the body or its organs of elimination (usually the kidneys and the liver) to remove drug from the blood or plasma. Clearance is a quantitative measure of the rate of elimination of a drug from the body. It is important to emphasize that clearance is not an indicator of how much drug is being removed; it only represents the theoretical volume of blood or plasma which is completely cleared of drug in a given period of time. The amount of drug removed depends on the plasma concentration of drug as well as the clearance. (See Figure 10)

Thus total drug removed = [plasma drug] and Clearance

---

**Pathway of excretion**

**Mechanism**

**Examples**

**Excretion pattern**

---

**Clearance (CL)**

- Refers to a drug’s rate of elimination by all routes, normalized to the concentration (C) of the drug in biological fluid (such as blood or plasma):
  - \( CL = \text{rate of elimination} / C \)
  - \( CL = V_d \times Kel \)
  - \( CL = V_d \times (0.693 / t_{1/2}) \)

- Units on clearance are volume per unit time (ex. L/hr)

- Systemic clearance is additive, and is a function of elimination by all participating organs:
  - \( CL_{\text{systemic}} = CL_{\text{renal}} + CL_{\text{hepatic}} + CL_{\text{other organs}} \)
Clearance - Renal

- Renal clearance determines the rate of elimination of unchanged drug and metabolites.
- Dependent upon:
  - Properties of the drug itself:
    - Water solubility, ionization state, protein binding
  - Physiological parameters of the kidney:
    - pH, rate of filtration, rate of secretion, blood flow, & number of functional nephrons.

Clearance - Hepatic

- Hepatic clearance contributes to the rate of elimination following metabolic transformation of the parent drug to metabolites.
- Since this type of elimination is usually not "saturable," the rate of elimination by the liver is typically 1st order and directly proportional to drug concentration.
- Factors affect hepatic clearance include:
  - Induction of hepatic enzymes (by other drugs or by self)
  - Presence of hepatic disease, patient age, and genetic polymorphisms in hepatic enzymes.

Factors affect drug clearance

- Body weight: Proportional to liver or kidney size. Need adjustment by STDS = 70 kg or 1.73 m².
- Body surface area: Need adjustment by STDS = 70 kg or 1.73 m².
- Plasma protein binding: [protein binding] × [free drug] × CI.
- Extraction ratio: High extraction drug has reduced [free plasma drug].
- Renal function: Needless to say.
- Hepatic function: Will affect blood flow to kidney and liver.
- Cardiac output: Will affect blood flow to kidney and liver.
- The elimination process can be expressed by two mathematical expressions.

Drug elimination

Elimination Rate Constant (Kd)

The elimination rate constant, Kd, is the fraction or percentage of the total amount of drug in the body removed per unit of time and is a function of clearance and volume of distribution:

$$ K_d = \frac{C_l}{V_d} $$

*Eq. 27*

Kd is also referred as Kel

1st Order (non-saturating) Kinetics

- Most drugs exhibit 1st order kinetics.
- A constant fraction of drug is eliminated per unit time.
- The fraction of the dose eliminated in a given time is independent of the dose.
- The amount of drug elimination is equal to the plasma drug concentration multiplied by the drug clearance (Cl x [Drug]).
- The t½ and clearance of the drug remain constant as long as renal and hepatic function do not change (it is independent of amount of drug presented).
First order elimination
The fraction of the drug that is removed at any time remain constant.
It is dependent on plasma concentration.

\[ \frac{dC_p}{dt} = -k \]

The rate of decrease is independent of concentration, depend only on k.

Zero Order Kinetics
A few drugs (such as ethanol) exhibit zero-order kinetics.
The rate of drug elimination is constant and is independent of the plasma drug concentration.

Saturating kinetics:
In some cases, drugs exhibit zero-order elimination at high doses; the reason that the rate of drug elimination becomes constant is that the elimination process becomes saturated.

Zero order elimination
The same amount of the drug is disappeared at a given amount of time regardless how much drug is presented.

\[ \text{[Plasma] reduction by } 0.5 \text{ also reduce elimination time by half} \]

Examples include alcohol, phenytoin, salicylate metabolism. It is enzyme saturable.

Concentration-Dependent Kinetics
1st Order Kinetic at low drug concentration region
Zero-Order Kinetic at high concentration region

Half-life (t½)
• The time required for a drug to drop to half of its original conc.
• Reflect how efficiently the clearance organs are functioning
  - Dictate how frequently the drug must be given
    - 2 hr in most antibiotics vs. 2 d in Phenobarbital
  - \( t \frac{1}{2} \) of a drug mainly excrete by liver would not change significantly by kidney disease, and vice versa (hepatic elimination process is not directly affected by renal function)

When choose drugs for animals with renal or liver dysfunction, knowledge of major elimination route become very important in choosing the drug.
The elimination half-life ($t_{1/2}$) for a given drug is calculated using the drug’s elimination rate constant $K_e$:

$$t_{1/2} = \frac{0.693}{K_e}$$

The half-life of a drug can be affected by:
- disease states: which can affect $V_d$ and $C_l$
- patient age: which can affect $V_d$

**Drug elimination ($t_{1/2}$)**

C = $C_0 \cdot e^{k_c \cdot t}$

for $t = t_{1/2}$ → $C = \frac{C_0}{2} \Rightarrow \frac{\ln C}{\ln 2} = \ln C_0 - k_t \cdot t_{1/2}$

$\ln C = \ln C_0 - k \cdot t_{1/2}$

$t_{1/2} = \frac{0.693}{k}$

LEARN!

$t_{1/2}$ is the time it takes for C to drop to half of its value

**Relationship between $t_{1/2}$ and $K_e$**

IV dose $\rightarrow$ Central $\rightarrow$ Peripheral

$t_{1/2} = \frac{0.693}{K_e + K_{renal} + K_{hepatic} + ...}$

**Accumulation Factor**

A. With repeating drug doses, a drug will accumulate in the body until dosing ceases.
B. Practically, accumulation will be observed if the dosing interval is less than 4 half-lives.
C. Accumulation of the drug is inversely proportional to the fraction of the dose lost in each dosing interval:

Accumulation factor = $1 / (1 - \text{Fraction of drug remaining})$
Steady state concentration (Css)

Css occurs during:
1. constant infusion when the infusion rate = the rate of elimination.
2. Repeated dosing until all plateau and trough conc become the same.

The steady-state drug plasma concentration can be calculated using the following formula:

\[ \text{Css} = \frac{(D \times F)}{(K_e \times V_d) \times T_m} \]

where:
- \( D \) = dose of drug administered
- \( T_m \) = dosing interval (in hours)

Derive the Css Formula

To maintain a steady-state, the drug eliminated should be replenished by the maintenance dose, either by constant infusion or repeated doses.

When using infusion: Maintenance dose = \( C_l \times \text{Css} \)

When using repeated doses:
- Dose = \( D \times F = C_l \times \text{Css} \times T_m \)
- \( = K_e \times V_d \times \text{Css} \times T_m \)

Rearrange for \( \text{Css} \),

\[ \text{Css} = \frac{(D \times F)}{(K_e \times V_d) \times T_m} \]

Determination of IV infusion rate

Goal: achieve a desired steady-state level.

Rate of infusion must equal rate of elimination

\[ \text{Rate of infusion} = (K_e \times V_d) \times \text{Css} \]

\[ \frac{mg/hr}{1hr \times L} \times \frac{L}{mg/L} = C_l \times \text{Css} \]

Maintenance infusion rate =

Loading dose =

Relation of \( \frac{1}{2} \) to Css (Plateau principle)

For constant infusion and 1st order elimination (assumption), how quick a drug reaches steady state is determined by the drug’s elimination rate \( (K_e) \) and can be expressed by \( \frac{1}{2} \)

One \( \frac{1}{2} \) = 50% Css
Two \( \frac{1}{2} \) = 75% Css (50%+25%)
Three \( \frac{1}{2} \) = 87.5% Css (50%+25%+12.5%)
Four \( \frac{1}{2} \) = 97% Css (50%+25%+12.5%+6.25%)

General Rule:

Time required for a drug to reach steady state= Five \( \frac{1}{2} \)

Relation of \( \frac{1}{2} \) to Css (Plateau principle)

After the infusion begins or stopped at a specific time point, it will take 3-5 \( \frac{1}{2} \) from that point to reach steady state
Think about it?

Can a higher maintenance dose (without a loading dose) resulted in quicker time to reach steady state?

Ie. can 100 mg bid reach steady state quicker than 50 mg bid?

NO, NO, NO, NO, NO

Higher dose only resulted in higher blood conc and more drug elimination, it still required 5 t ½ to reach steady state

I.e. time to reach steady state will be THE SAME, but Higher dose will have higher peak and trough

Example question #1

The data in Table 10-9 represent the average findings in antibiotic plasma samples taken from 10 human (average weight 70 kg), tabulated in a four-lecture.

**Table 10-9: Comparison of Plasma Concentrations of Antibiotic, as Related to Dosage Form and Time**

<table>
<thead>
<tr>
<th>Time After Dose (hr)</th>
<th>IV Solution (µg/ml)</th>
<th>Oral Solution (µg/ml)</th>
<th>Oral Tablet (µg/ml)</th>
<th>Oral Capsule (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>30.0</td>
<td>15.0</td>
<td>7.5</td>
<td>3.75</td>
</tr>
<tr>
<td>1.0</td>
<td>10.0</td>
<td>5.0</td>
<td>2.5</td>
<td>1.25</td>
</tr>
<tr>
<td>2.0</td>
<td>5.0</td>
<td>2.5</td>
<td>1.25</td>
<td>0.625</td>
</tr>
<tr>
<td>3.0</td>
<td>2.5</td>
<td>1.25</td>
<td>0.625</td>
<td>0.3125</td>
</tr>
<tr>
<td>4.0</td>
<td>1.25</td>
<td>0.625</td>
<td>0.3125</td>
<td>0.15625</td>
</tr>
<tr>
<td>5.0</td>
<td>0.625</td>
<td>0.3125</td>
<td>0.15625</td>
<td>0.078125</td>
</tr>
<tr>
<td>6.0</td>
<td>0.3125</td>
<td>0.15625</td>
<td>0.078125</td>
<td>0.0390625</td>
</tr>
<tr>
<td>7.0</td>
<td>0.15625</td>
<td>0.078125</td>
<td>0.0390625</td>
<td>0.01953125</td>
</tr>
<tr>
<td>8.0</td>
<td>0.078125</td>
<td>0.0390625</td>
<td>0.01953125</td>
<td>0.009765625</td>
</tr>
<tr>
<td>9.0</td>
<td>0.0390625</td>
<td>0.01953125</td>
<td>0.009765625</td>
<td>0.0048828125</td>
</tr>
<tr>
<td>10.0</td>
<td>0.01953125</td>
<td>0.009765625</td>
<td>0.0048828125</td>
<td>0.0024414063</td>
</tr>
</tbody>
</table>

**Example question #2**

Metoclopramide was given to a patient in a 5 mg IV bolus dose. Plasma conc were determined to help establish an optimal dose regimen.

1. What is the order of the decay?
2. Estimate the initial conc of the drug?
3. What is the half-life of the decay?
4. What is the rate constant of the decay?
5. What is the Vd of this patient?
6. How long will it take to eliminate 87.5% of the dose?
Example question #3
Lidocaine infusion.
$C_{ss} = 2 \text{ mg/L, } t_{1/2} = 80 \text{ min, } V_d = 0.7 \text{L/kg}$
Find 1. infusion rate, 2. loading dose

Solution:
1. Infusion rate =

2. Loading dose =

Example question #4
A patient (70kg) is to take 2 doses per day of sulfamethoxazole ($t_{1/2} = 10 \text{ hr}$) to maintain a $C_{ss}$ of 3 $\mu$g/ml in a $V_d$ of 0.2 L/kg. What is the maintenance dose?

$CI = Ke_t \times V_d$

Pharmacokinetic Practice Questions
1. Amikacin is eliminated by the kidney with a Clearance of 1 ml/min*kg, from a $V_d$ equivalent to the ECF (0.2 L/kg). What is the plasma half-life for a 50 kg person?
   A. 12 sec  B. 1 min  C. 50 min  D. 2.5 hrs  E. 15 hrs

Pharmacokinetic Practice Questions
2. The half-life of carbenicillin in its $V_d$ (0.2 L/kg) is 1 hr. If a constant IV infusion of 700 mg/hr is begun, approximately how long will it take for the plasma conc to reach a steady state level of 100 mg/L in a 50 kg adult?
   A. 4 hrs  B. 8 hrs  C. 12.3 hr  D. 20 hrs  E. 24 hrs

Pharmacokinetic Practice Questions
3-1. What is the IV loading dose required to raise the theophylline plasma level from 5 mg/L to 15 mg/L in a 50 kg adult? The $V_d$ of theophylline is 0.5 L/kg
   A. 5 mg  B. 50 mg  C. 250 mg  D. 500 mg  E. 2.5 mg

Pharmacokinetic Practice Questions
3-2. In the previous problem, what is the maintenance infusion rate required to achieve a steady state plasma theophylline level of 15 mg/L in the 50 kg adult? The $CI$ is 0.04 L/hr*kg
   A. 0.6 mg/hr  B. 2 mg/hr  C. 30 mg/hr  D. 300 mg/hr  E. 750 mg/hr
3-3. In the previous problem, what is the required dosing interval for oral administration of a 250 mg tablet assuming rapid and complete absorption?

A. 0.8 hr  B. 4.8 hr  C. 8 hr  D. 12.5 hr  E. 25 hr

4. For a zero-order elimination, the time it takes for the plasma level of a drug to fall below the therapeutic level is:

A. The half-life for elimination
B. Directly proportional to the logarithm of the initial plasma concentration
C. Dependent upon the Michaelis constant of the metabolizing enzyme
D. Directly proportional to the initial plasma concentration
E. Directly proportional to the reciprocal of the initial plasma concentration

5. A patient has a plasma level of 24 mg/L of a drug with a first order elimination rate constant of 0.2 per hr. How long will it take for the plasma level to decrease to 3 mg/L assuming no more drug is given?

A. 1 hr  B. 2 hr  C. 5 hr  D. 8 hr  E. 11 hr

6. It is desired to maintain a plasma conc of 150 μg/ml of carbenicillin in a 70 kg person with normal renal and hepatic functions. Calculate the necessary IV infusion rate. The t½ is 1 hr and Vd is 0.18 L/kg.

7. The following plasma conc (mg/100ml) of a toxic substance were obtained at various times (hr) after admission to the hospital:

<table>
<thead>
<tr>
<th>Time after dose (hr)</th>
<th>Plasma conc. (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>16.6</td>
</tr>
<tr>
<td>8</td>
<td>12.6</td>
</tr>
<tr>
<td>12</td>
<td>9.7</td>
</tr>
<tr>
<td>16</td>
<td>6.9</td>
</tr>
<tr>
<td>20</td>
<td>4.0</td>
</tr>
<tr>
<td>24</td>
<td>1.2</td>
</tr>
</tbody>
</table>

What is the order of the elimination? Assuming that this poison has a Vd of 41 L, what was the rate of appearance of the substance from the whole body in the time period: 1) 0-5 hr; 2) 5-10 hr? (Draw a Plot)

8. A single dose of 400 mg of the sulfamethoxazole was administered IV to a 70 kg adult. At various times the following plasma conc were observed:

<table>
<thead>
<tr>
<th>Time after dose (hr)</th>
<th>Plasma conc. (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>15</td>
<td>7</td>
</tr>
</tbody>
</table>

A. Calculate the initial plasma conc
B. Find the rate constant for elimination of sulfamethoxazole
C. What is the clearance of sulfamethoxazole in this person
Pharmacokinetic Practice Questions

9. A drug is eliminated from the plasma by the following 1st order pathways at the rate constant given:
   Excretion through the bile, $K_{bile} = 0.6 \, \text{hr}^{-1}$
   Metabolism, $K_{met} = 0.25 \, \text{hr}^{-1}$
   Excretion by the kidney, $K_{renal} = 0.05 \, \text{hr}^{-1}$
   A. What is the plasma half-life of the drug?
   B. What is the plasma half-life if the metabolism of the drug is completely blocked?
   C. What is the ratio of the drug found in feces to that found in urine?

10. A patient (70 kg) with meningitis was given a continuous IV infusion of benzylpenicillin. The plasma t1/2 is 30 min and the Vd is 0.2 L/kg:
   A. What is the rate of infusion required to maintain the plasma conc at 20 ug/ml?
   B. How long will it take to reach 87.5% of the steady state level at the rate of infusion starting from 0?
   C. What is a suitable loading dose to allow a rapid plasma conc of 20 ug/ml?

Pharmacokinetic Practice Questions

11. Digitoxin is eliminated very slowly from the body; the t1/2 is about 7 days in adult. The Vd is 0.5 L/kg and the therapeutic effective plasma conc is about 20 ng/ml.
   11-1. Calculate the loading dose of digitoxin for a 70 kg person.
   11-2. Calculate the Clearance of this person?
   11-3. Find the daily maintenance dose of digitoxin for a 70 kg person.
   11-4. Rely solely on daily maintenance dose, how long will it take to reach 90% of the therapeutically effective plasma conc?

Pharmacokinetic Practice Questions

11. Digitoxin is eliminated very slowly from the body; the t1/2 is about 7 days in adult. The Vd is 0.5 L/kg and the therapeutic effective plasma conc is about 20 ng/ml.
   11-5. Why is recovery from toxicity slow with digitoxin?
   11-6. The daily dose is very low, what’s the advantage and disadvantage of taking the doses every other day?
   11-7. The patient calls to say he forgot the dose yesterday, Do you advise double the dose to make up for yesterday?
TVBS 一步一脚印，发现新台湾～有机养殖～

96年3月4日

• 我的猪不打针
• 吃牧草的鸡
• 江医师的鱼
• 中草药及健康配方(herbal nutrient)

藥物殘留對於人體危害之舉例

以公共衛生之觀點，長期食用藥物殘留量超過法定容許標準之畜禽產品，對人類可能之傷害舉例包括：

1. Chloramphenicol引起骨髓幹細胞障礙導致再生不良性貧血、顆粒性白血球減少症及血小板減少症。
2. Penicillins與纖孢子素類Cephalosporins可能引起過敏性反應。
3. 依達特作用，如Furazolidone、Diethylstilbestrol。
4. 致畸胎作用，如Pyrimethamine。
5. 不論預防或治療之用，長期或濫用抗菌劑可能會誘發抗藥性菌株之產生，若感染人類，可導致選擇可用之抗菌劑種類變少。

藥物殘留之定義

• 藥物殘留係指：預防或治療動物疾病、所授予動物體內之動物用藥品；2. 用於促進生長、改善飼料利用率之效率，所授予動物體內之含藥物飼料添加物；3. 或因環境汙染因素而攝入動物體內之化學物質；其以原形態或代謝物聚積貯於動物之細胞、組織或器官稱之。

• Any compound present in the edible tissues of the target animal that results from the use of the sponsored compound, including the sponsored compound itself, its metabolites, and any substances formed in or on food as the result of the use of the sponsored compound

藥物殘留之種類

1. 動物用藥品
2. 含藥飼料添加物
3. 農藥
4. 環境污染物質

1. 動物用藥品：
A. 抗菌劑類：如Streptomycin、Oxytetracycline、Erythromycin等抗生素類，及Enrofloxacin與Sulfamethoxazole等人工合成抗菌劑。
B. 抗寄生蟲劑類：如Dichlorvos、Ivermectin等。
C. 抗黴菌劑類：如Nystatin（已於94年7月被刪除）
D. 荷爾蒙藥物：如Zeranol
3. 農藥：如有機氯化合物Aldrin、Dieldrin、Lindane等及有機磷化合物Malathion、Parathion等。
4. 環境污染物：如有放射性物質及重金屬毒物（砷、汞、銅、鉛、鋁、鉻等）。

藥物殘留之種類

2. 含藥飼料添加物
A. 抗菌劑類：如Carbadox、Chlortetracycline、Neomycin、Sulfamethazine等。
B. 防疫用藥物：如Amprolium、Monensin、Salinomycin等。
C. 抗過敏劑類：如Nystatin（已於94年7月被刪除）
D. 荷爾蒙類：如Zeranol
3. 農藥：如有機氯化合物Aldrin、Dieldrin、Lindane等及有機磷化合物Malathion、Parathion等。
4. 環境污染物：如有放射性物質及重金屬毒物（砷、汞、銅、鉛、鋁、鉻等）。

動物用藥品在畜產品中的殘留容許量

最大殘留量(Maximal Residue Level, MRL)或耐受量(Tolerance Level, TL)

• 指殘留於畜產品(肉、禽、乳品)中之藥物，其被允許之最大殘留量或濃度。
• 在此殘留量以下之藥物，被視為對人體健康之不良影響極低。
• MRL或TL常以ppm或ppb表示。

藥物殘留對於人體危害之舉例

以公共衛生之觀點，長期食用藥物殘留量超過法定容許標準之畜禽產品，對人類可能之傷害舉例包括：

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4. 致畸胎作用，如Pyrimethamine。
5. 不論預防或治療之用，長期或濫用抗菌劑可能會誘發抗藥性菌株之產生，若感染人類，可導致選擇可用之抗菌劑種類變少。

藥物殘留之定義

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• Any compound present in the edible tissues of the target animal that results from the use of the sponsored compound, including the sponsored compound itself, its metabolites, and any substances formed in or on food as the result of the use of the sponsored compound

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3. 農藥：如有機氯化合物Aldrin、Dieldrin、Lindane等及有機磷化合物Malathion、Parathion等。
4. 環境污染物：如有放射性物質及重金屬毒物（砷、汞、銅、鉛、鋁、鉻等）。
殘留量之表示方法

百萬分之一 (part per million; ppm)
每公斤猪肉中殘留1毫克之某藥物，即表示該藥物於豬肉中之残留量為1 ppm (1 mg/kg or 1 μg/g)。

十億分之一 (part per billion; ppb)
若每升生乳中殘留1微克之青黴素，即表示該牛乳中含1 ppb (1 μg/L or 1 ng/mL)之青黴素。

殘留容許量之訂定

• 依據最敏感之實驗動物（通常是小白鼠或大白鼠）之亞急性毒性試驗（90天）或慢性毒性試驗（104週以上）結果，求出藥物對實驗動物最大安全量（No Observed Effect Level, NOEL）後，再除以對人體之安全係數，以求得該藥物對人體之可被接受之每日攝取量（Acceptable Daily Intake; ADI）換算而成。

• 安全係數在亞急性毒性試驗數據為2000倍，在慢性毒性試驗數據時為100倍。即在老鼠試驗中投藥90天所獲得的最大安全量的二千分之一或投藥兩年所獲得的最大安全量的百分之一就是人體每天可攝食的安全量。

Human Food Safety Requirements

• FDA guideline requires knowledge of
  – Toxicology
  – Residue Chemistry
  – Microbial Food safety

Food Safety Decisions

✓ No Observed Effect Level (NOEL)
  Determined from toxicity test results

✓ Safety Factors

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Safety factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic</td>
<td>100</td>
</tr>
<tr>
<td>Reproduction/Teratology</td>
<td>100–1000</td>
</tr>
<tr>
<td>90-Day</td>
<td>1000</td>
</tr>
</tbody>
</table>

Acceptable Daily Intake (ADI)

\[
ADI = \frac{\text{No Observed Effect Level (NOEL)}}{\text{Safety Factor}}
\]

Safe concentration = \[
\frac{\text{ADI (μ g/kg/day) } \times 60 \text{ kg}}{\text{Consumption Values (grams consumed/day)}}
\]
Consumption Values for average Americans

<table>
<thead>
<tr>
<th>Edible products</th>
<th>Gram consumed/day (g/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>300</td>
</tr>
<tr>
<td>Liver</td>
<td>100</td>
</tr>
<tr>
<td>Kidney</td>
<td>50</td>
</tr>
<tr>
<td>Fat</td>
<td>50</td>
</tr>
<tr>
<td>Eggs</td>
<td>100</td>
</tr>
<tr>
<td>Milk</td>
<td>1500 mL</td>
</tr>
</tbody>
</table>

Establishing a Withdrawal Time

- Run a residue depletion study under field use conditions selecting sampling times on the terminal elimination phase of the depletion curve closest to the tolerance

Establishing a Withdrawal Time

- Maximum conditions of use
  - Highest dose
  - Longest duration of treatment
- 20 animal design
- 4-5 animals per sampling (slaughter) point
- 4-5 equally spaced sampling times
- Calculate the 99th percentile statistical tolerance limit with 95% confidence

訂定動物用藥品之停藥期

- 動物用藥品之停藥期是依據零殘留量或殘留容許量訂定。一般而言，具有致癌性或致畸胎性的藥品，不設殘留容許量，其停藥期則是依結果達到殘留容許量所需時間訂定。

- 停藥期之訂定為藥物殘留期間加上安全期間。所謂殘留期間為最後一次投藥後，可食組織中之藥物殘留濃度降低至殘留容許量或無法檢測出殘留的期間。安全期間則因實驗動物毒性試驗結果而異。

訂定動物用藥品之停藥期

安全期間:
- 實驗動物致癌性試驗證實：
  - 具有致癌性者其安全期間為殘留期間之二倍
  - 具有致畸胎性者為殘留期間之一倍
  - 其他動物用藥品為殘留期間之二分之一倍
- 停藥期應按實足天數並無條件進位計算，例如停藥5.3天，係最後投藥之時間算起，須經6天才供屠宰，但牛乳之停藥期則按實足小時數計算。
動物用藥品之正確使用方法

✓ 確實遵守停藥期、乳汁捨棄期及使用之劑量規定，才能使食品中之殘留量合法。

• 禽畜屠宰時其體內的殘留量必須達殘留容許量以下，因此應嚴格遵守自禽畜停止攝食飼料添加物或停止接受藥物治療至准予屠宰的這一段停藥期。

• 數種以上飼料添加物合併使用時其停藥應以其中最長之停藥期為準。

• 藥物依推薦之對象動物使用，不可使用於未指示之動物。

• Thiamphenicol在國內僅核准添飼、肌注、皮注於豬(60kg以下)及雞(產蛋雞除外)，國外則另可使用於牛及綿羊。曾有動物藥品販賣業者擅自在山羊身上使用，其賠償責任應歸屬販賣業者，而與製藥廠無關，因其標籤上並未註記可使用於山羊。

• Carbadox使用對象僅指示用於豬，不可任意使用於雞;carbadox在11-28ppm飼添時具提高豬增重速率及改進飼料利用率之效，但對雞無此功效;在50-55ppm時主要用於控制赤痢螺旋體引起的赤痢，但該病原體不侵襲雞。

• Maduramicin僅用於肉雞而不可使用於產蛋雞，因為此藥物會經由胎盤進入蛋內。

• Sulfaquinoxaline等為葉酸代謝拮抗劑(與葉酸的前驅體PABA相拮抗)，會導致pyrimidines合成受阻，巨母紅血球DNA無法製造，引起禽畜巨母紅血球性貧血。因此使用劑量不宜過高，於病原微生物獲得控制後應予停藥，並於飼料中補充葉酸。

• Arsanilic acid在50-100ppm可提高增重速率及改進飼料利用率、增加種雞及產蛋雞產蛋率。但飼料中含1000ppm時即會抑制禽畜生長，2000ppm或以上時更可引發高死亡率。

動物用藥品之正確使用方法

✓ 依指示使用藥品，否則可能導致失效或中毒。

• Tiamulin不可與離子型球蟲藥(如monensin、narasin、maduramicin、semduramicin、salinomycin及lasalocid等)併用，併用時對禽畜之運動能力具不良之影響而導致死亡。

• Maduramicin不可使用於產蛋雞，使用於雞以外的動物，可能引起危險，與tiamulin及furazolidone三者不可同時使用。

• Furaltadone*：行政院農業委員會92年11月公告，自93年6月1日起全面禁止動物使用硝基夫喃類之動物藥品;包括furazolidone、furaltadone、nitrofurazone、nifurstyrenate等。

動物用藥品之正確使用方法

✓ 依指示推薦劑量使用，否則可能導致失效或中毒。

• Sulfaguanidine等為葉酸代謝拮抗劑(與葉酸的前驅體PABA相拮抗)，會導致pyrimidines合成受阻，巨母紅血球DNA無法製造，引起禽畜巨母紅血球性貧血。因此使用劑量不宜過高，於病原微生物獲得控制後應予停藥，並於飼料中補充葉酸。

動物用藥品之正確使用方法

✓ 熟讀注意事項並依指示實施給藥。

• Lincospectin有散劑與肌肉注射劑兩種不同劑型，有些獸醫師為增高投藥劑量，故意購入散劑後加水予以溶解，實行肌肉注射。此舉會對動物造成許多不良的影響，因散劑並未滅菌且溶解後的容易亦未經熱原試驗，未調整pH值等;緊急性，導致動物可能會發生注意力不集中、緊張、癱瘓等病變，對於已染病的動物更是加深其緊迫。

動物用藥品之正確使用方法

✓ 不任意混和兩種以上之藥物投藥。
動物用藥品之正確使用方法

勿自行添加未經核准以及未經臨床證實藥效之藥物

β-agonist為交感神經興奮劑，亦具能減少體脂並促進動物體生長之效果，然而至目前為止大部分國家均未允許其為生長促進劑之用，勿自行添加。

【注】

β1作用：心機能亢進、促進脂肪分解；
β2作用：平滑肌鬆弛、促進肝醣分解。

β1副作用：對有心血管疾患之病人如高血壓者會誘發腦溢血；有狹心症與鬱血性心衰竭者會因心臟工作負荷過度而心跳停止。

β2副作用：增高血糖而加重糖尿病等。

動物用藥品之正確使用方法

• 非飼料添加之治療藥物，必須由獸醫師親自處方及監督使用。

In conclusion:

 避免ELUD (Extra-Label Use of Drugs)

任何未依標籤指示的用藥皆可歸類為ELUD

動物用藥品之正確使用方法

在結論：

 避免ELUD (Extra-Label Use of Drugs)

任何未依標籤指示的用藥皆可歸類為ELUD

藥物殘留標準

<table>
<thead>
<tr>
<th>畜禽種類</th>
<th>殘留部位</th>
<th>殘留容許量 (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahbactin</td>
<td>牛、豬、栄</td>
<td>0.1</td>
</tr>
<tr>
<td>Albendazole</td>
<td>牛、羊</td>
<td>0.1</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>牛、羊</td>
<td>0.05</td>
</tr>
</tbody>
</table>

共約120項藥品請參考
動物用藥殘留標準（農委會網頁）

備註

• 註1. 表中乳汁之殘留容許量單位為mg/L。
• 註2. 兩魚、蝦以大同填塞後去除殘存Oxytetracycline，而不得殘留Chlorotetracycline及Tetracycline。
• 註3. 本標準所列之魚及蝦種種類係指行政院農業委員會訂定之動物用藥品管理法之水產動物用藥品使用規範指定對象水產動物。
• 註4. Sulfadimethoxine與Sulfamonomethoxine兩者殘留量合計不得高於0.1 ppm。

藥物殘留標準是一個經常動態更新的資料庫

由於抗生素等動物用藥問題已成國際焦點，加上分析方法之不斷進步，各國對於禽畜水產食品之衛生安全標準及檢測限制等之要求逐漸嚴格，美國、歐盟等國對進口食品中殘留之抗生素等動物用藥之規定日益嚴格。日本近來也因此大幅修訂其動物用藥殘留標準，自從日本由泰國進口的蝦、蟹相繼檢出氯黴素，大陸銷歐盟的蝦及吳郭魚被檢出有Enrofloxacin，以及美國及歐盟對我國禽畜水產品之質量日趨嚴格，因此對各國變動中的標準，應該有機動性的了解。
藥物殘留標準是一個經常動態更新的資料庫

✔ 世界各國經常會依其國家的經濟情況、社會文化等因素，在殘留方面訂立適合自己國情的耐受藥量(Tolerance Level)和殘留停藥期(Drug Withdrawal Time)
✔ 日本訂定最嚴格的「零」殘留或至少訂出「最低可能」的允許殘留量，例如磺胺劑(Sulfamethazine)必須在0.05 ppm以下。
✔ 瑞典為防止抗生素在肉品的殘留，更全面禁止抗生素或抗菌劑在飼料中長期使用。

自2006年5月開始，日本決定對所有食品中可能的農藥、動物用藥及飼料添加物的殘留基準(MRL)予以正面表列。目前暫定的殘留基準中共有647種，其中農藥約400種，動物用藥及飼料添加物有200多種，水產品用藥品20種。但尚未完成所有品目檢驗方法的建立，已訂有MRL的農藥目前有229種，動物用藥30種。此正面列表法預計每五年檢討修正一次。

對未列安全殘留量者採用“一律基準”，EU, Japan 0.01 ppm, Canada and New Zealand 0.1 ppm, USA 0.01-0.1 ppm。

半衰期乘數(HLM)

• 半衰期乘數(HLM)數是基於組織樣品(ETH)的有效半衰期，HLM= the number of half-lives contained within the WDT to reach tolerance level

∴: the smaller the HLM, the longer the estimated tissue t ½

背景

• ELUD could potentially lead to violative residues in food animals. An appropriately extended WDI is essential to food safety.
• Ideally, the extended WDI should be calculated on the basis of tissue 1% of the drug. HOWEVER, these data are not readily available.
• The use of HLM has been proposed as a simple alternative method to estimate the effective tissue t ½ (ETH).
• Extended WDI estimated using various HLMs, were compared with the WDI calculated using actual tissue t ½.

一般規則

1. Ten t ½ could render > 99.95% of the drugs reduced to below tolerance level (or MRL).
2. A common practice among vet practitioners is to assume that for the majority of the drugs, 5 t ½ (97%) is required for tissue concent to be depleted to below MRL.

Feasibility of using half-life multipliers (HLM) to estimate extended withdrawal intervals (WDI) following the extralabel use of drugs (ELUD) in food-producing animals

R. Gehring, RE Baynes, AL Craigmill and JE Riviere

Journal of Food Protection, vol. 67, No. 3, 2004
Relationship between time required to deplete drug to tolerance when the dose is doubled versus when the underlying tissue $t_{1/2}$ is doubled

Estimated tissue half-lives (ETH) for selected drugs using various half-life multipliers (HLMs)

\[ \text{ETH} = \frac{\text{WDT}}{\text{HLM}} \]

Target concentration and half-lives for marker residues of selected drugs in target tissues

\[ \text{ETH} = \frac{\text{WDT}}{\text{HLM}} \]

Comparison of extended WDI calculated using a HLM of 5 with different safety factors and using actual tissue $t_{1/2}$

Comparison of extended WDI calculated using the two different estimates of the tissue $t_{1/2}$
Comparison of extended WDI after addition of safety factor to HLM calculated $t_{1/2}$

Conclusions

- For drugs with short $t_{1/2}$ (<36 hrs), an HLM=5 is probably adequate.
- For drugs with longer $t_{1/2}$ (>100 hrs), an HLM=3 is more adequate.
- HLM of 3 should be considered if a more conservative estimate is required. Or, a safety factor should be added when use HLM=5.