PHARMACODYNAMICS

The study of the relationship between the concentration of a drug and its pharmacological effect.
DRUG-DOSING REGIMEN

• Route of administration
  • Galenic formulation
  • Unit dose
  • Frequency
  • Loading dose
  • Length of treatment
Dosage \rightarrow \text{Plasma Concentration} \rightarrow \text{Site of Action} \rightarrow \text{Effects}

\text{Pharmacokinetics} \leftrightarrow \text{Pharmacodynamics}
PHARMACODYNAMICS (PD) a drug effect on the body over a time-course

- **E MAX**: MAXIMAL EFFECT ATTAINABLE DUE TO THE DRUG

- **EC50**: The concentration at which half of the maximal effect is observed – **DRUG POTENCY**.

\[
\text{EFFECT} = \frac{\text{E}_{\text{MAX}} \cdot \text{CONCENTRATION}}{\text{EC50} + \text{CONCENTRATION}}
\]
ERYTHROPOIETIN AND ANEMIA

Eschbach et al. NEJM 316:73-8, 1987
METFORMIN DOSE-RESPONSE

Diabetic peripheral neuropathy - Pain

1) The recommended dose of duloxetine for the treatment of neuropathic pain associated with diabetic peripheral neuropathy is 60 mg orally once daily. The maximum recommended dose is 60 mg once daily. **There is no evidence that doses higher than 60 mg/day provide additional significant benefit.** A lower starting dose may be considered for patients in whom tolerability is a concern. Efficacy beyond 12 weeks of treatment has not been evaluated in placebo-controlled trials [1].
DOSE-EFFECT PARAMETERS

**Potency:** The sensitivity of an organ or tissue to the drug

**Efficacy:** The maximum effect
Table 3 – Equivalent statin doses

<table>
<thead>
<tr>
<th>Lovastatin</th>
<th>Pravastatin</th>
<th>Simvastatin</th>
<th>Fluvastatin</th>
<th>Atorvastatin</th>
<th>Rosuvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg</td>
<td>20 mg</td>
<td>10 mg</td>
<td>40 mg</td>
<td>--</td>
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<tr>
<td>40 or 80 mg</td>
<td>40 mg</td>
<td>20 mg</td>
<td>80 mg</td>
<td>10 mg</td>
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</tr>
<tr>
<td>80 mg</td>
<td>80 mg</td>
<td>40 mg</td>
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<td>20 mg</td>
<td>5 or 10 mg</td>
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<td>--</td>
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<td>80 mg</td>
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<td>40 mg</td>
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<td>80 mg</td>
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<td>--</td>
<td>--</td>
<td>--</td>
<td>40 mg</td>
</tr>
</tbody>
</table>

**Statins—Dose Response**

Response to Minimum/Maximum Statin Dose

- Fluvastatin 20/80 mg: 19/31
- Pravastatin 20/80 mg: 27/37
- Lovastatin 20/80 mg: 28/40
- Simvastatin 20/80 mg: 12/47
- Atorvastatin 10/80 mg: 37/55

COMPARING DOSE-EFFECT CURVES

% of Maximal Effect

[Drug]

Drug A

Drug B

Drug C
HOW IS PD EFFECT ACHIEVED?

Drug concentration in plasma or tissue fluid drives a **reversible** interaction with a protein:

- receptor,
- enzyme,
- ion channel
DRUG RECEPTOR INTERACTIONS
LOCUS OF ACTION "RECEPTORS"
- Bound ↔ Free

TISSUE RESERVOIRS
- Free ↔ Bound

Systemic Circulation
- Free Drug
- Bound Drug

Absorption → Free Drug

Excretion → Free Drug

Biotransformation → Bound Drug
**DRUG-RECEPTOR INTERACTIONS**

- **Drug**
- **Receptor**
- **Drug-Receptor Complex**
- **Ligand-binding domain**
- **Effector domain**

The interaction is modeled with kinetic constants $k_1$ and $k_2$.
DRUG–RECEPTOR BINDING

rate dependent on the concentration of the drug and receptor, and the resulting *drug–receptor complex* breaks down at a rate proportional to the number of complexes formed

\[ [D] + [R] \xrightleftharpoons[k_1]{k_2} [DR] \]

\[ k_1 = \text{association rate constant} \]
\[ k_2 = \text{disassociation rate constant} \]

\[ K_A = \text{association equilibrium constant} = \frac{[DR]}{[D][R]} \]

\[ K_D = \text{disassociation equilibrium constant} = \frac{[D][R]}{[DR]} = \frac{1}{K_A} \]

FIGURE 3.3

Mass-action equations describing reversible interaction between a ligand (drug, toxin) and a receptor.
MAXIMUM BINDING CAPACITY

radioligand displacement from a receptor as non-radioactive ligand increases
RECEPTOR OCCUPANCY MODELING

- attempts to link the action of a drug to the proportion of receptors occupied by that drug at equilibrium

- insulin stimulates maximum glucose oxidation in adipocytes with only 2-3% of receptors bound

- LH stimulates maximum testosterone production in Leydig cells when only 1% of receptors are bound
WHY ARE THERE SPARE RECEPTORS?

• allow maximal response *without* total receptor occupancy – increase sensitivity of the system

• spare receptors can bind (and *internalize*) extra ligand preventing an exaggerated response if too much ligand is present

The receptor theory assumes that all receptors should be occupied to produce a maximal response. In that case at half maximal effect EC50=kd. Sometimes, full effect is seen at a fractional receptor occupation
RECEPTOR-MEDIATED EFFECTS

% Maximum Effect

[Drug]

Agonist
Partial agonist
Antagonist
AGONISTS

Stimulate the response from the receptor

drugs that interact with and activate receptors; they possess both affinity and efficacy

two types

**Full** – an agonist with maximal efficacy

**Partial** – an agonist with less than maximal efficacy
Mrs Winslow's Soothing Syrup

For children teething. Greatly facilitates the process of Teething, by softening the gums, reducing all inflammation; will allay ALL PAIN and spasmodic action, and is SURE TO REGULATE THE BOWELS. Depend on it, Mothers, it will give rest to yourselves and RELIEF AND HEALTH TO YOUR INFANTS. Sold by all chemists, at 1s 1/2d per bottle.

Source: http://www.opioids.com/images/soothingsyrup.html
METHADONE

pure mu-agonist

differs from morphine by an additional noncompetitive antagonist activity at the N-methyl-D-aspartate (NMDA) receptor
Buprenorphine hydrochloride is a derivative of the morphine alkaloid thebaine.
ANTAGONISTS

Antagonists interact with the receptor but do **NOT** change the receptor; they have affinity but **NO** efficacy.

There are two types:

- **Competitive** – **NALOXONE**
- **Noncompetitive** – **OMEPRAZOLE**
RECEPTOR DOWN REGULATION

- continued use and stimulation of receptors by agonist drugs may decrease the **number and sensitivity** of receptors

- Constant use of beta-2 agonist salbutamol inh reduces therapeutic response in ASTHMA
RECEPTOR UP REGULATION

• continued use and inhibition of receptors by antagonists may increase the number and sensitivity of receptors

• Sudden withdrawal of propranolol may precipitate angina
TOLERANCE AND DEPENDENCE

Tolerance – it is increasing of the dose of a drug required to produce the same effect.

It occurs rapidly with opioids (with morphine 12–24 hours, e.g. the hot plate test – in mice, after 3 days the dose of morphine required for analgesia increases 5-fold).

Important in drug addiction – may need to increase dose 50-fold.
WHY DOES TOLERANCE OCCUR?

There are several potential reasons:

- Increased metabolism of the drug
- Decreased receptor affinity
MECHANISMS OF DRUG ACTION
GENERAL CATEGORIES

• Physical/chemical (Mannitol, oral antacids)
  • alter, respectively, osmolarity and pH, but do not interact directly with cellular processes.

Biological

• **Receptor interaction** - alters the receptor protein’s three-dimensional structure, triggering *signal transduction* processes within the cell and resulting in a biological effect
• **Non-receptor interaction** - directly target enzymes, carrier proteins like ion transporters, ion channels, DNA, and cellular structures like microtubules.
1. Agonist → Na → Activation of conductance
2. Agonist → G-Protein Activation → Generation of Second Messenger → Activation of Cell Signaling
3. Agonist → Phosphorylation of Tyrosines on Key Signaling Molecules → Activation of Cell Signaling
4. Agonist → Transport to the Nucleus → Activation of transcription and translation
ENZYME INHIBITORS

Mechanism of how Methotrexate inhibits cell growth by competing with folate acid.
ENZYME INHIBITORS

Cyclooxygenase enzymes

Arachidonic acid

COX-1
• Constitutive
• Normal tissue
• Housekeeping functions

COX-2
• Inducible
• Inflammation
• Pain
• Cancer

PGH₂

PGE₂, PGF₂α, PGD₂, PGI₂, TX

Prostanoids
(Prostaglandins, thromboxanes)
DIRECT INHIBITORS OF ION CHANNELS
DRUGS INHIBITING MEMBRANE ION TRANSPORTERS
DRUGS INTERACT WITH DNA

- Cell Wall Synthesis
  - D-cycloserine
  - Vancomycin
  - Bacitracin
  - Penicillins
  - Cephalosporins
  - Cephamycins

- Cell Wall Integrity
  - β-lactamases

- DNA Synthesis
  - Metronidazole
  - DNA Gyrase
  - Quinolones

- RNA Polymerase
  - Rifampicin

- DNA Replication
- DNA Transcription
- Translation

- Ribosomes
- Cytoplasmic Membrane
  - Phospholipid Membranes
  - Polymyxins

- Protein Synthesis
  - 50S Inhibitors
    - Erythromycin
    - Chloramphenicol
    - Cindamycin
    - Lincomycin
  - 30S Inhibitors
    - Tetracyclines
    - Streptomycin
    - Spectinomycin
    - Kanamycin
ADVERSE DRUG REACTIONS
THERAPEUTIC AND TOXIC EFFECTS

% Responding vs Dose

100
90
80
70
60
50
40
30
20
10
0

Therapeutic
Toxic

ED<sub>50</sub>
ED<sub>99</sub>
TD<sub>1</sub>
TD<sub>50</sub>

Dose

70 80 90 100

200 300
ADVERSE REACTIONS

Side Effects

• Expected responses based on the pharmacologic action of the drug

Allergic Reactions

• Exaggerated immune response to a certain drug

Organ Cytotoxic Effects

• Adverse effects on organs
ADVERSE REACTIONS

Idiosyncratic Reactions

• Reaction that is particular to an individual or defined group of people

Drug-drug Interactions

• Interaction of 2 or more drugs that result in a disadvantage to a patient

Drug-food Interactions

• Interaction of a drug with food that results in an adverse patient reaction
A Population Pharmacokinetic–Pharmacodynamic Model for Simvastatin that Predicts Low-Density Lipoprotein-Cholesterol Reduction in Patients with Primary Hyperlipidaemia

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