REVIEW ON PRINCIPLES OF DRUG ACTIONS

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Drug Receptor Interaction

Don’t Panic

Simple Occupancy Theory

Simple occupancy theory: “Intensity of response to a drug is proportional to the number of receptors occupied by that drug”

- Maximal response occurs when all available receptors have been occupied
- This theory is not able to explain why one drug is more potent than another if they bind to the same receptor and both bind maximally to all receptors? (Example: Demerol vs Talwin)

Theories of Drug-Receptor Interaction

What are receptors?
Traditional model was a rigid one:
- “Lock and Key”
  - Lock → Receptor surface
  - Key → Drug or Ligand
Theories of Drug-Receptor Interaction

- Receptors → fluid, flexible surfaces or pockets
- Can change 3-D structure as ligand docks
- Occupy small portion or surface of a macromolecule
- Ligand - Receptor docking → structure changes

![Inactive and Active Receptors](image)

HOW TO EXPLAIN EFFICACY?

Drug (D)

![CONFORMATIONAL SELECTION](image)

SPARE RECEPTORS

- The receptor theory assumes that all receptors should be occupied to produce a maximal response. In that case at half maximal effect $EC_{50}=K_d$. Sometimes, full effect is seen at a fractional receptor occupation – spare receptors
- Allow maximal response without total receptor occupancy – increase sensitivity of the system
- The number of receptors may exceed the number of effector-molecules available
- Receptor remains activated after agonist departs: more than one receptor is activated

![Spare Receptors Diagram](image)

Main Receptor Classes

- Agonist
- N3
- Generation of second messengers
- Activation of cell signaling
- Transduction into the nucleus
- Activation of transcription and translation

![Main Receptor Classes Diagram](image)

DOSE-RESPONSE RELATIONSHIPS

To determine the quantitative relation between drug concentration and response

![Dose-Response Curve](image)

Characteristics of A Dose-Response Curve

- Maximum Effect or Efficacy
- Potency ($EC_{50}$)
- Variability

![Characteristics of A Dose-Response Curve Diagram](image)
Types of Dose-Response Curves: Graded

Graded:
Dose related to magnitude on a graded scale

PDE Inhibition
Theophylline [µM]

Potency: Quantal Responses

Achieving Complete Analgesia
ED_{50} = 490 mg
ED_{90} = 400 mg

Total Lidocaine Dose (mg)

Dose-Response Curves and Efficacy

Relative Safety of A Drug

- Dose-response curves help estimating the safety of a drug
- Therapeutic Index: TI = LD_{50}/ED_{50}
  * LD_{50} = the median lethal dose of a drug in animals
  * Statement on selectivity of desired effects vs toxic

Comparison of Dose-Response Curves

Effect
A (Lethality) Potency
A > B > C

Efficacy
A = C > B

Safety (TI)
A > B

Antagonist Effects on Dose-Response Curves

A) Competitive Antagonists
Antagonist Effects on Dose-Response Curves

B) Non-Competitive Antagonists

FACTORS MODIFYING DRUG DOSE-RESPONSE RELATIONSHIP

Predictable Influencing Factors

BODY SIZE

AGE

GENDER

ROUTE OF ADMINISTRATION

TIME OF ADMINISTRATION

PATHOLOGICAL STATE

TOLERANCE

GENETIC FACTORS

PRESENCE OF OTHER DRUGS

Drugs and Age of Patients

Changes in Body Proportions with Age

<table>
<thead>
<tr>
<th>Minerals</th>
<th>2.0%</th>
<th>3.2%</th>
<th>4.2%</th>
<th>5.3%</th>
<th>4.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>12.0%</td>
<td>13.4%</td>
<td>17.3%</td>
<td>16.0%</td>
<td>17.6%</td>
</tr>
<tr>
<td>Water</td>
<td>80.0%</td>
<td>61.2%</td>
<td>64.8%</td>
<td>60.0%</td>
<td>54.0%</td>
</tr>
<tr>
<td>Fat</td>
<td>5.0%</td>
<td>13.4%</td>
<td>13.7%</td>
<td>13.0%</td>
<td>18.0%</td>
</tr>
</tbody>
</table>

Elder (85 kg) | 2.0% | 3.2% | 4.2% | 5.3% | 4.0% |

Age-Dependent of Diazepam Elimination

Elimination half-life of Diazepam is shortest in the infant and longest in the elderly.
PATHOLOGICAL STATE & DRUGS

• Pathophysiology: how disease affects responses to drugs
  • Kidney
    – Reduce drug excretion: drugs accumulate in body
    – Must decrease dosage of drug until kidney function back to normal
  • Liver
    – Site of drug detoxification and metabolism
    – Drug will accumulate to toxic levels in body

Drugs and Fetal Development

Drug Therapy During Pregnancy and Breastfeeding

• Physiological changes in pregnancy that impact drug dosing are in the:
  – Kidney
  – Liver
  – Gastrointestinal tract
• All drugs cross the placenta
• Drug transfer is
  – Easier—lipid soluble drugs
  – Difficult—ionized, highly polar or protein-bound drugs

Food & Drug Effects

GENETIC POLYMORPHISMS

Pharmacokinetic
• Transporters
• Plasma protein binding
• Metabolism

Pharmacodynamic
• Receptors
• Ion channels
• Enzymes
• Immune molecules
Atypical Plasma Cholinesterase

- Atypical plasma cholinesterase has 1/100 the affinity for succinylcholine as normal enzyme
- Occurs in 1:2500 individuals

% inhibition

- Typical
- Atypical

normal enzyme inhibited > 70%
abnormal inhibited < 30%

log molar dibucaine conc.

Adapted from: Pharmac Ther 47:35-60, 1990.

ETHNIC DIFFERENCES IN THE DISTRIBUTION OF ACETYLATOR PHENOTYPE

<table>
<thead>
<tr>
<th>Population</th>
<th>% Slow</th>
<th>% Hetero Fast</th>
<th>% Homo Fast</th>
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</thead>
<tbody>
<tr>
<td>South Indians</td>
<td>59</td>
<td>35.6</td>
<td>5.4</td>
</tr>
<tr>
<td>Caucasians</td>
<td>58.6</td>
<td>35.9</td>
<td>5.5</td>
</tr>
<tr>
<td>Blacks</td>
<td>54.6</td>
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</tr>
<tr>
<td>Eskimos</td>
<td>10.5</td>
<td>43.8</td>
<td>45.7</td>
</tr>
<tr>
<td>Japanese</td>
<td>12</td>
<td>45.3</td>
<td>42.7</td>
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<tr>
<td>Chinese</td>
<td>22</td>
<td>49.8</td>
<td>28.2</td>
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</tbody>
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Preclinical Safety and Toxicology Testing

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<tr>
<th>Preclinical Safety Studies</th>
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Clinical Trials: Main Questions

- Phase I
  - What are the side effects?
  - Is it safe enough to test?

- Phase II
  - Does it work at all?
  - What is the dosage range?

- Phase III
  - Is it better than placebo?
  - Is it better than other treatments?
  - What are the side-effects?

Problem

Which drug would you choose to send to Phase I trials based on the following preclinical data:

1. Drug A: TI = 100 - T1/2 = 10 min in rodents
2. Drug B: TI = 10 - T1/2 = 90 min in rodents
3. Drug C: TI = 90 - T1/2 = 2 min & Rapidly metabolized to OH-C
Laws Regulating Manner of Drugs Dispensing

- The Durham-Humphrey Amendment of 1952
  - Establish "legend" drugs: "Cautions: Federal laws prohibits dispensing without prescription"
  - Prescriptions refill
  - Recognized the OTC drugs

- Controlled Substances Act in 1970
  - Classified controlled substances into schedules (flexible)
  - Requires that prescribers and dispensers register with the Drug Enforcement Agency (DEA)

Schedules

- **Schedule I**: Highest abuse potential, **no medical** use in the U.S.
- **Schedule II**: High abuse potential, but, **may be used medicinally**
- **Schedule III**: Limited dependence potential
- **Schedule IV**: Lower abuse potential than I & II
- **Schedule V**: Lowest potential for abuse
- **Schedule VI (Virginia)**: All legend drugs not included in other schedules