CLINICAL PHARMACOLOGY

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GENERAL PRINCIPLES

DRUG NOMENCLATURE

- ❑ chemical name: describes the chemical structure, the same in all countries
- ❑ drug company code: a number, usually for drugs that are not sold
- ❑ non-proprietary name: shortenend form of chemical name, listed in pharmacopea
- ❑ proprietary name: the brand name or registered trademark
- ❑ street name: drugs of abuse

PHASES OF CLINICAL TESTING

- ❑ phase I: healthy humans in hospitals, kinetics and dynamics are known
- ❑ phase II: unhealthy humans: small studies, not blinded
- ❑ phase III: double blind, hundreds of people, comparing new drug to standard of care
- ❑ phase IV: wide distribution, patients closely monitored

DRUG ADMINISTRATION AND SITE OF ACTION

- ❑ different routes of administration are chosen depending on
  - desired onset of action
  - systemic or local effects
  - patient characteristics
  - properties of the drug

Table 1. Routes of Drug Administration

Route	Advantage	Disadvantage
Oral (PO)	Convenient Large surface area for absorption	Drug metabolism Incomplete absorption First pass effect Gastrointestinal (GI) upset
Intravenous (IV)	Direct No first pass effect Slow infusions or rapid onset of action Easier to titrate dose	Requires IV access Hard to remove Vascular injury, exctra-vasation
Intra-arterial	To specific organs, e.g. brain, heart	
Intramuscular (IM)	Good for depot storage (if oil based) Rapid onset of action	Pain at site of injection
Subcutaneous (SC)	Non irritating small volumes Even slow absorption Adrenaline in local anesthetics	Pain at site of injection
Topical	Convenient Localized Limited systemic absorption	Effects are limited to area of application
Inhalation	Immediate action in lungs Rapid delivery to blood Local or systemic action	Must be in gas, vapor or aerosol form
Buccal	Rapid onset of action No first pass effect	Must be lipid soluble
Transdermal	Direct application Rapid onset of action	Irritation at site of application Delayed onset of action
Others: Intrathecal, Intraperitoneal, Rectal		

PHARMACOKINETICS (ADME)

- ❑ **"ADME": absorption, distribution, metabolism, excretion**
- ❑ definition: the manner in which the body handles a drug
- ❑ examines the rate at which drug concentrations change in the body by observing
  - input processes
    - **absorption**: movement of drug into the body from the site of administration
  - output processes: responsible for drug delivery and removal from the body
    - **distribution**: movement of drug from intravascular to extravascular compartment
    - **metabolism**: chemical transformation of drug
    - **elimination**: removal of drug from the body

ABSORPTION

PRINCIPLE: The amount of drug that reaches the systemic circulation (bioavailability) is highly dependent on absorption. Properties of the drug, route of administration and patient factors should be considered to ensure clinical effectiveness.

- ❑ most drugs are absorbed into the systemic circulation via passive diffusion
- ❑ other mechanisms of absorption include: active transport, facilitated diffusion, pinocytosis/phagocytosis
- ❑ absorption rate and amount depends on
  - local blood flow at admininstration site
    (eg. sublingual vessels provide significant blood flow therefore rapid absorption)
  - lipid solubility: greater lipid solubility = increased rate of diffusion through membranes
    - e.g. anesthetics are very lipid soluble therefore have a rapid onset of action
  - molecular size: small size, water soluble drugs can pass through channels in membranes, large molecules cannot
    - e.g. aminoglycosides are large molecules and are not absorbed through intestinal mucosa and are therefore not orally active
  - local pH and drug ionization: charged molecules do not cross membranes
    - e.g. lactulose ionizes ammonia to ammonium and keeps it in the bowel
  - total surface area for absorption: the small intestine has villi which increase the surface area for absorption, and hence is the primary site of absorption for most oral drugs

Bioavailability

- ❑ the percentage of dose given that reaches the systemic circulation in unchanged form
- ❑ the administered dose does not equal active dose
- ❑ drugs with a low bioavailability may be ineffective orally
  - e.g. pencillin G is destroyed by gastric enzymes and needs to be administered IV
- ❑ fate of oral drug: GI Tract —> portal vein —> liver (metabolism) —> systemic circulation

First Pass Effect

- ❑ metabolism of orally administered drug in the liver before it reaches the systemic circulation
- ❑ significant first pass metabolism limits a drug's bioavailability
- ❑ drugs with a high first-pass effect include: chlorpromazine, levodopa, morphine, propranolol, lidocaine, hydralazine, nortriptyline, and organic nitrates
- ❑ drugs with low hepatic extraction (little or no first pass effect) include: diazepam, digoxin, phenylbutazone, phenytoin, theophylline, tolbutamide, warfarin

PRINCIPLE: Some drugs have uncommon distribution parameter (e.g. Vd, protein binding, storage in fat depots) and have to be dosed carefully to avoid toxicity while ensuring therapeutic efficacy.

- ❑ definition: process by which drugs are carried throughout the body to reach target sites of action

Volume of Distribution (Vd)

- ❑ actual volume of distribution (Vd): the anatomic volume that is accessible to drug, e.g. total body water of 40 L
- ❑ apparent volume of distribution (Vd) is a calculated value that does not correspond to an anatomical space, a drug with a large Vd (larger than 40 L) must distribute in other tissues besides body water
  - e.g. Amiodarone; Vd=400L in a 70kg person

Protein Binding
- ❑ drug molecules in the blood are in two forms:
  - bound to plasma proteins, mainly albumin
  - free
- ❑ principles of protein binding
  - only free drug can distribute into tissues and exert its action, and is subject to metabolism and elimination
  - affinity of a protein binding site for a drug determines bound/unbound concentrations, and reversibility of interaction
  - saturation of binding sites may result in a large increase in unbound drug concentration, which could cause toxicity
  - if albumin concentration is decreased (liver failure or nephrotic syndrome), dose of highly bound drug must be lowered to avoid toxicity
  - competition for binding sites between drugs and endogenous substrates can result in interactions and toxicity
  - significant drug interactions can occur due to competitive protein binding
    - e.g. ASA displaces several drugs which are highly bound to plasma proteins such as phenytoin, increasing risk of toxicity
  - in general, only drugs that are highly protein bound, e.g. > 90%, are involved in drug interactions due to competitive binding

Depots
- ❑ a part of the body (e.g. a type of tissue) where drug molecules tend to be stored
- ❑ fat tends to be a depot for very lipid soluble drugs (e.g. diazepam)

Barriers
- ❑ body structures that limit/prevent diffusion of drug molecules,
- ❑ e.g. blood-brain barrier (BBB), placenta

Table 2. Examples of Important Highly Protein Bound Drugs

Name	% Bound
Salicylic Acid	82
Phenytoin	90
Propranolol	93
Diazepam	99
Warfarin	99.5

Table 3. Organ Distribution of Drug Metabolizing Enzymes

Site	Relative Activity
Liver	100
Lung	20-30
Kidney	8
Intestine	6
Term Placenta	5
Adrenal Glands	2
Skin	1

METABOLISM (BIOTRANSFORMATION)

PRINCIPLE: Drugs that are metabolized by similar enzymes, eg. the same cytochrome P450 isoenzymes, have the potential to interfere with each other's metabolism. When in doubt, especially for new drugs, look up metabolic route and then anticipate the interaction before writing the prescription.

- ❑ conversion of a drug into another form may result in
  - activation of pro-drug: eg. codeine to morphine, nitroglycerine to NO
  - maintenance of activity, eg. diazepam is metabolized to an active metabolite
  - inactivation, eg. procaine to PABA
- ❑ main site of biotransformation in the body is the LIVER.
- ❑ drug metabolizing enzyme pathways generally mediate 2 types of reactions
  - Phase I reactions
    - oxidation-reduction and hydrolysis
    - introduce or unmask polar chemical groups therefore increase water solubility
    - mediated by cytochrome P450 enzymes
    - P450's are found in the endoplasmic reticulum or cell cystoplasm
  - phase II reactions
    - conjugation with polar endogenous substrates e.g. glucoronic acid, glutathione
    - increases water solubility and renal elimination

Clinical Pearl
- ❑ **Cytochrome P450 isoenzyme CYP 3A4 metabolizes about 50% of all drugs, hence if a drug which is metabolized by 3A4 is prescribed, double check for possible interactions if any other drug is added to the regimen.**

Drug Interactions are Often Due to Interactions in Biotransformation Pathways

❑ Phase I (Cytochrome P450 enzymes)

1. erythromycin inhibits the CYP3A4 enzyme, and predisposes to cisapride toxicity and possible fatality
2. cimetidine inhibits P450 enzymes, leading to increased levels of theophylline, diazepam, warfarin, phenytoin
3. phenobarbital induces P450 enzymes, which could decrease levels of other drugs (see below: Enzyme Induction)
4. the SSRIs could inhibit CYP 2D6 (and 3A4), and therefore increase serum levels of other drugs metabolized by these enzymes, e.g. benzodiazepines, carbamazepine, phenytoin
5. the new HIV drugs, the protease inhibitors, are metabolized by cytochrome P450 enzymes, (e.g. indinavir is metabolized by CYP 3A4), and hence could interact with other drugs metabolized by this route

❑ Phase II (Conjugation reactions):

1. Acetaminophen is 95% metabolized to inactive glucuronic acid and sulfate conjugates, and 5% oxidized by P450, generating a reactive metabolite which is then conjugated with glutathione. If glutathione stores are depleted, eg. massive dose of acetaminophen, the reactive metabolite remains unconjugated and causes hepatocellular damage. In concurrent ingestion of alcohol and large doses of acetaminophen, a double whammy situation occurs. Alcohol induces the P450 enzymes, and hence the generation of the reactive metabolite; alcoholics tend to be deficient in nutrients, notably glutathione, hence depletion occurs more readily, resulting in massive hepatocellular damage in this situation

❑ Enzyme Induction

- over 200 unrelated drugs have the ability to increase the activity of drug biotransforming enzymes generally reducing activity/intensity of drug action
- reflects de novo synthesis of P450 and other biotransforming enzymes
- induction of P450 can stimulate multiple iso-enzymes specifically or non specifically

Table 4. Examples of Inducing Agents

Inducing Agent	Substance whose metabolism is increased
Phenobarbital	Bilirubin
DDT	Chlorpromazine
Phenytoin	Codeine
Glutethamide	Cortisol
Phenylbutazone	Estradiol, meperidine, morphine, testosterone, thyroxine

❑ other factors affecting drug metabolism

- age
  - early in fetal life drug metabolizing enzyme levels are low
  - elderly have reduced rates of metabolism due to reduced hepatic function
- nutrition
  - inhibition or drug metabolizing enzymes with decreased protein, decreased fatty acids
- alcohol, vitamin deficiency states
  - induction of P450 with chronic ingestion
  - inhibition of P450 with acute ingestion
- radiation
- sex
- race

Clinical Pearl

❑ **The very young and the very old are very sensitive to the actions of drugs.**

ELIMINATION

PRINCIPLE: Dosing of drugs needs to be adjusted according to the elimination characteristics of the patient (e.g. in renal impairment) in order to avoid toxicity from drug or metabolite accumulation.

- ❑ routes of elimination include
  - stool (e.g. corticosteroids from biliary system)
  - lungs (e.g. general anesthetics eliminated by expiration)
  - skin and mucous membranes (e.g. rifampin in tears)
- ❑ KIDNEYS are the main organ of drug excretion through
  - glomerular filtration: passive, pore size about 400-600 Angstroms
  - tubular secretion: active, against concentraion gradient, saturable, two distinct transport mechanisms for weak acids and weak bases
    - e.g. acids: penicillin, salicyclic acid, probenecid, chlorothiazide
    - e.g bases: quinine, quaternary ammonium compounds (e.g. choline)
  - tubular reabsorption: can be active or passive (depending on charge)
- ❑ elimination rate depends on renal function (assessed clinically, using serum creatinine levels)
  - the Cockroft-Gault equation can estimate creatinine clearance (CrCl) for males as:

$$\text{CrCl (mL/min)} = \frac{(140\text{-patient's age in yrs}) \times \text{IBW (kg)}}{50 \times \text{SCr } (\mu\text{mol/L})}$$

  - for females above equation x 0.85

- ❑ drug interactions due to interference with filtration, secretion, reabsorption
  - probenecid significantly reduces renal excretion of penicillin by competing for the weak acid transport
  - lithium is renally eliminated through glomerular filtration, much of the filtered load is reabsorbed at the proximal renal tubule. Sodium competes for the reabsorption site with lithium. Hence, thiazide diuretics, which can cause hyponatremia and reduced sodium load in the renal tubule, increase the reabsorption of lithium and can predispose to increased serum lithium levels and lithium toxicity

PHARMACOKINETICS CALCULATIONS

- ❑ definition: the quantitative description of the rates of the various steps of drug disposition (ie.how drugs move through the body)
- ❑ the pharmacokinetic principles of ADME (absorption, distribution, metabolism and elimination) can be graphically represented on the concentration vs time graph (see Figure 1)

The Time Course of Drug Action

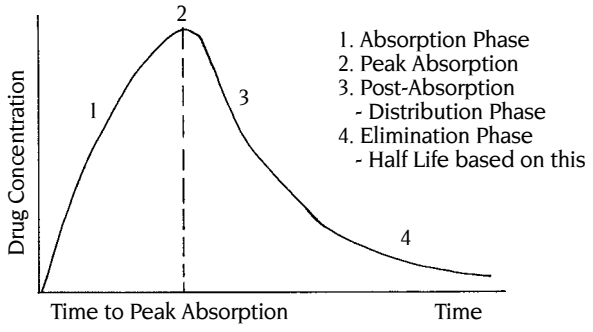


Figure 1. Time Course of Drug Action

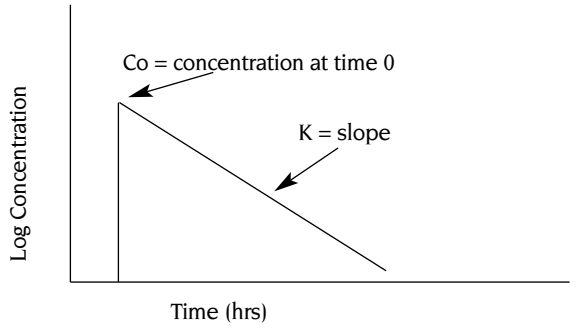


Figure 2. Log Concentration vs. Time Graph (IV bolus dose)

- ❑ many kinetic parameters are measured using IV dosing, there is no absorption phase, and distribution for most drugs is rapid, therefore the elimination is the main process measured.
- ❑ the concentration axis is converted to a log base 10 concentration to allow for easier mathematical calculations
- ❑ equations from the graph
  - t1/2 (Half-life) = the inverse of the slope of the line (k) x 0.693
  - Vd (volume of distribution) = dose/concentration at time 0
  - Cl (clearance) = k x Vd

Half-Life (t1/2)
- ❑ defined as the time it takes for blood level of a drug to fall to one-half (50%) of the level measured at some prior time
- ❑ for most drugs, half-life correlates with the elimination phase
- ❑ in general it takes 5 half lives to reach steady state with repeated dosing or for drug elimination once dosing is stopped

Steady State
- ❑ the concentration at which the same amount of drug entering the system is eliminated from the system
- ❑ time is important for therapeutic monitoring as drug levels are only reliable when the drug has reached this steady state
- ❑ any change in drug dose and interval will change the steady state level
- ❑ special situations
  - drug with long half-life and the need to rapidly increase blood levels – give a loading dose (e.g. phenytoin)
  - drugs with a very short half-life and the need for a long term effect – multiple, frequent repeated doses are too inconvenient thus use a continuous infusion (e.g. nitroprusside)

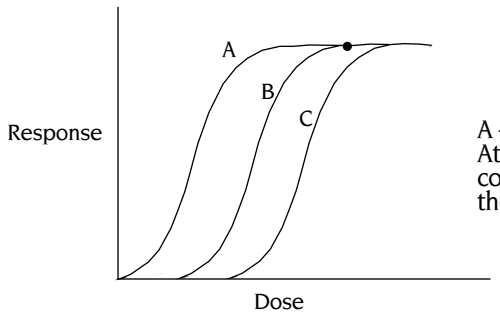
Elimination Kinetics
- ❑ first-order kinetics (the most common type)
  - a constant fraction of drug is eliminated per unit time
  - the amount of drug eliminated is based on the concentration of drug present
  - this relationship is linear and predictable
- ❑ zero-order kinetics (less common, associated with toxicities)
  - non-linear kinetics
  - a constant amount (number of molecules) of drug is eliminated per unit time
  - clearance slows as drug concentration rises
  - some drugs can follow first order kinetics until elimination is saturated (usually at large doses) and the clearance decreases
  - some drugs follow non-linear kinetics at therapeutic levels e.g. phenytoin

PHARMACODYNAMICS

- ❑ definition: the relationship between the drug concentration and effect (what the drug does to the body)

Agonists Have Two Main Properties
- ❑ affinity: the ability of the agonist to "bind to" the receptor
- ❑ efficacy: the ability to cause a response via the receptor interaction
- ❑ e.g. the β2-agonist (salbutamol) bind to β2-receptors (i.e. has affinity) and result in activation of smooth muscle relaxation (ie. has efficacy)

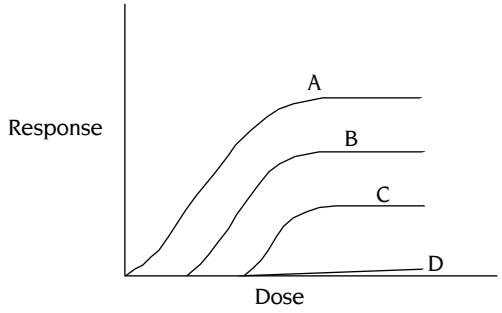
Antagonists
- ❑ have affinity (can bind to a receptor) but no efficacy
- ❑ chemical antagonism: direct chemical interaction between agonist and antagonist prevents agonist binding to receptor
  - e.g. chelator agents for removal of heavy metals
- ❑ functional antagonism: interaction of 2 agonists that act at different receptors independent of each other but have opposite physiological effects
  - e.g. acetylcholine at the muscurinic receptor decreases HR, constricts pupil, stimulates intestinal motility
  - epinephrine at the adrenergic receptor increases HR, dilates pupil, decreases intestinal motility
- ❑ competitive antagonism (most common in clinical practice) (see Figure 3)
  - antagonist acts at same receptor (i.e. binds) displacing agonist
  - antagonist binding is reversible and can be overcome



A —> C increasing level of antagonist.
At each dose of antagonist increasing the concentration of agonist can surmount the inhibition

Figure 3. The Log Dose-Response Curve for Competitive Antagonism

- ❑ non-competitive antagonism (see Figure 4)
  - irreversible binding of antagonist to receptor
  - allosteric effect: changes ability of the agonist to bind to the receptor through various mechanisms such as changing the conformation of the receptor
  - increasing concentrations of agonist cannot reverse the antagonism

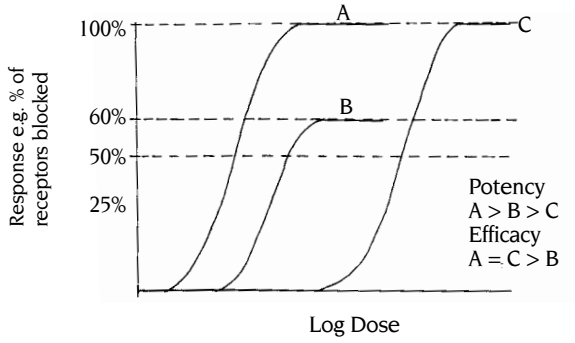


A —> D increasing dose of irreversible antagonist. With one dose of antagonist, increasing dose of agonist does not completely surmount antagonism as seen in B. Eventually with high enough antagonist concentrations, no amount of agonist can elicit a response as seen in D.

Figure 4. TIME: Log Dose Response Curve for Non-Competitive Antagonism

Dose-Response Relationship

- ❑ pharmacodynamic principles measuring efficacy and potency can be quantified using dose-response curves
- ❑ with gradual dose response relationships the response of the drug reflects the number of receptors that are effectively occupied
- ❑ efficacy
  - the maximum intensity of response to a drug, eg. if Drug A causes a greater maximum intensity of response than Drug B (regardless of dose), then Drug A is more efficacious than Drug B
  - ED50 (effective dose-50%) the dose or drug that gives rise to the designated response in 50% of the subjects
  - ED50 is easier to measure than maximum effect and is used to determine efficacy
- ❑ potency
  - a comparison of the ED50 of two or more drugs that have parallel log dose-response curves
  - the drug that reaches the ED50 at the lower dose is the more potent
  - potency is a term that is often misused (confused with efficacy)
  - potency is not important if you can increase the dose of the less potent drug without causing side effects

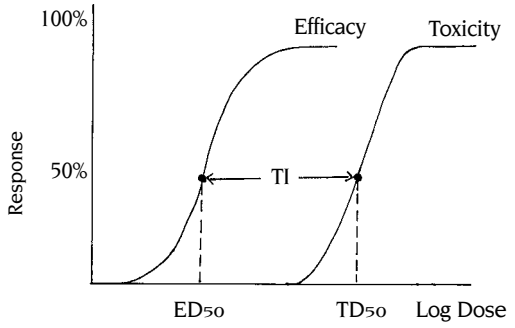


In the Log Dose-Response curve, the efficacy and potency of 3 different drugs are compared. Drug A and Drug C give a 100% response and are thus more efficaceous than Drug B. Drug B requires a lower dose than Drug C to give 50% response, so Drug B is said to be more potent than Drug C.

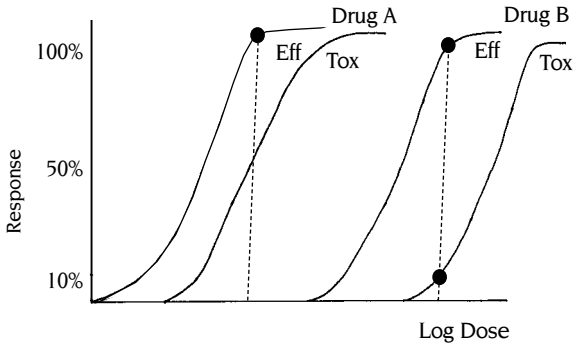
Figure 5. Log Dose-Response Curve Efficacy and Potency

Effectiveness and Safety

- ❑ the two most clinically relevant properties of any drug are effectiveness and safety
- ❑ effectiveness
  - similar to efficacy but in real populations (i.e. not experimental)
- ❑ safety (see Figure 6)
  - LD50 (lethal dose-50%): defined as the dose of a drug needed to cause death in 50% of a test population of subjects (e.g. usually rodents)
  - TD50 (Toxic Dose - 50%): defined as the dose needed to cause a harmful effect in 50% of the subjects



The therapeutic index (TD50/ED50) is a measure of the margin of safety of a given drug.



Drug A has a much narrower therapeutic index than Drug B. The dose of Drug A required to achieve a 100% therapeutic response will be toxic in 50% of patients. For Drug B, this is only 10%.

Figure 6. ED50, TD50 and the Therapeutic Index (TI)

Therapeutic Index (TI) (see Figure 6)
- ❑ defined as TD50/ED50
- ❑ reflects the "margin of safety" for a drug - the likelihood of a high dose causing serious toxicity/death
- ❑ the larger the TI, the safer a drug
- ❑ factors can change the ED50, LD50 or the TD50
  - presence of interacting drugs
  - changes in drug absorption, distribution, metabolism, elimination
  - e.g. amoxicillin has a large TI, therefore therapeutic monitoring is not needed, whereas warfarin has a small TI and must have accurate therapeutic monitoring

Variability in Drug Action

PRINCIPLE: not everyone experiences the same response to the same dose (route of adminstration, dosage interval, etc. may need to be adjusted in some cases).

- ❑ some common causes of variable responses to a drug
  - age: (see geriatric pharmacology)
    - gastric pH and gut motility (affects absorption of certain drugs)
    - body composition (changes in fat, muscle, water content)
    - plasma protein levels (affects various aspects of pharmacokinetics)
    - renal, liver function (affects excretion and metabolism respectively)
  - gender: mainly due to presence or absence of certain enzymes, hormones, etc.
  - genetics: presence/absence of one or more genes needed to form enzymes, other proteins, hormones, etc.
  - overall health - presence/absence of other diseases
  - use of other drugs (i.e. interactions)
  - nutritional status - excess or deficiency of key vitamins, minerals, etc.
  - compliance

ADVERSE DRUG REACTIONS (ADRs)

- ❑ classification of adverse drug reactions
  - type A: predictable
  - type B: unpredictable

Type A
- ❑ side effects: excessive but characteristic pharmacological effect from usual dose of a drug
- ❑ overdose / toxicity: exaggerated but characteristic pharmacological effect from supratherapeutic dose
- ❑ teratogen: drug may produce developmental defects in fetus
- ❑ characteristics
  - account for 80% + of all ADRs
  - extension of pharmacological effect
  - dose-related and generally not severe
  - usually do not require discontinuation
  - dose reduction or titration may help minimize effect
  - e.g. a common side effect of beta-blockers is bradycardia (an extension of its therapeutic effect)

Type B
- ❑ idiosyncratic: uncharacteristic response to drug, unrelated to pharmacology
- ❑ pseudoallergenic: mimics immune-mediated reaction
- ❑ allergic / immune-mediated: does not occur on first exposure (up to 7d), immediate with subsequent exposure, may occur with low dose, resolves within 3-4 days of discontinuation
  - characteristics
  - usually more severe
  - usually require discontinuation
  - not dose-related
  - e.g. sulpha based drugs (such as septra) can cause an idiosyncratic Stevens Johnson Syndrome (SJS)

Approach to Suspected ADRs
- ❑ history and physical examination: symptoms, timing, risk factors, medication related, dechallenge and rechallenge information is needed, look up previous reports in the literature
- ❑ differential diagnosis: therapy or disease pathophysiology
- ❑ treat the adverse drug reaction: stop the drug, supportive care, symptomatic relief

PHARMACOKINETIC CALCULATIONS

❑ Volume of Distribution (Vd)
Vd = dose/concentration at time 0

❑ $\lambda = \frac{\text{rise}}{\text{run}}$

$= \frac{\log (C1 - C2)}{t_2 - t_1}$

❑ Clearance (CL)
CL = k x Vd

❑ Half-life (t1/2) = 0.693 x 1/k

❑ Ideal Body Weight (IBW)
for males = 50 kg + [2.3kg x (no. of inches > 5 ft)]
for females = 45.5 kg + [2.3kg x (no. of inches > 5 ft)]

❑ Loading Dose (LD)
LD = IBW x dose/kg
or
LD = Cp x Vd/F where Cp = target plasma drug concentration
Vd = volume of distribution
F = bioavailability (F = 1 for IV drugs)

❑ Maintenance Dose (MD)
MD = IBW x Dose per kg/τ (dosing interval)
For renally impaired:
MD = CrCl (patient)/ CrCl (normal) x Dose for normal patient
or MD = Cp x CLcr/ F

AUTONOMIC PHARMACOLGOY
- ❑ atuonomic nervous system (ANS) is divided into sympathetic and parasympathetic branches
- ❑ efferent fibers originate in nuclei in the CNS
- ❑ sympathetic preganglionic fibers exit the CNS through thoracic and lumbar spinal nerves and terminate in
  1. paravertebral ganglia that lie in a chain along the vertebral column - sympathetic trunk
  2. prevertebral ganglia
- ❑ parasympathetic preganglionic fibers exit through cranial nerves and sacral nerves and terminate on ganglion cells located near or within the innervated organs
- ❑ most organs are innverated by both sympathetic and parasympathetic nerves having opposing effects (see Table 1)
- ❑ all preganglionic fibers release acetylcholine which acts on
  - preganglionic fibers to all ganglia in the ANS and adrenal medulla
  - postganglionic parasympathetic fibers to effector organs
  - postganglionic sympathetic nerves to sweat glands
- ❑ postganglionic fibers release either acetylcholine or norepinephrine

Parasympathetic Nervous System

- ❑ acetylcholine is the neurotransmitter of the parasymathetic nervous system
- ❑ acetylcholine receptors include
  - nicotinic located in autonomic ganglia, adrenal medulla and neuromuscular junction (NMJ)
  - muscarinic
    - M1 located in the CNS
    - M2 non-neuronal receptors located on smooth muscle, cardiac muscle and glandular epithelium
- ❑ acetylcholines action is terminated by metabolism in the synaptic cleft by acetylcholine esterase and in the plasma by butyrocholinesterase
- ❑ parasympathomimetics can be divided into three groups
  1. choline esters e.g. carabachol, methacholine
  2. alkaloids e.g. pilocarpine
  3. anticholinesterases e.g. neostigmine

Sympathetic Nervous System (SNS)

- ❑ norepinephrine is the major neurostransmitter of the SNS
- ❑ receptors include
  - β1 predominately in cardiac tissue
  - β2 predominately in smooth muscle and glands
  - α1 predominately on post-synaptic receptors in smooth muscles and glands
  - α2 predominately on pr-synaptic terminals as well as post-synaptic terminals in the brain, uterus and vascular smooth muscle
- ❑ each receptor has a different sensitivity to sympathomimetics
- ❑ norepinephrines actions terminated by reuptake into the nerve terminal, diffusion from the synaptic cleft, metabolism

Table 5. Direct Effects of Autonomic Nerve Acitivity of some Organ Systems

Organ	Effect Of			
	Sympathetic		Parasympathetic	
	Action	Receptor	Action	Receptor
Eye				
Iris				
Radial Muscle	Contracts	α1	–	–
Circular Muscle (iris)	–	–	Contracts - miosis	M
Ciliary Muscle	(Relaxes)	β	Contracts - near vision	M
Heart				
Sinoartial (SA) Node	Accerlerates	β1	Decrease HR	M
Atria	Increases	β1	Decreases (contractility)	M
Atrioventricular (AV) Node			Decrease in conduction	
Blood Vessels				
Skin, Splanchnic Vessels	Contracts	α	–	–
Skeletal Muscle Vessels	Relaxes	β2	–	–
	(Contracts)	α	–	–
	Relaxes	M	–	M
Lung				
Bronchiolar Smooth Muscle	Relaxes	β2	Contracts	M
Bronchiolar Glands			Increased secretions	M
Gastrointestinal (GI) Tract				
Smooth Muscle				
Wall	Relaxes	α2β2	Contracts	M
Sphincters	Contracts	α1	Relaxes	M
Secretion	–	–	Increases	M
Myenteric Plexus	Inhibits	α	–	M
Genitourinary (GU) Smooth Muscle				
Bladder Wall				
Sphincters	Relaxes	β2	Contracts	M
uterus, Pregnant	Contracts	α1	Relaxes	M
	Relaxes	β2	–	–
Penis, Seminal Vesicles	Contracts	α	–	–
	Ejaculation	α	Erection	M
Skin				
Pilomotor Smooth Muscle	Contracts	α	–	–
Sweat Glands				
Thermoregulatory			Increases	M
Apocrine (stress)	Increases	α	–	–
Metabolic Functions				
Liver	Gluconeogenesis	α/β2	–	–
Liver	Glycogenolysis	α/β2	–	–
Fat Cells	Lipolysis	α2/β1	–	–
Kidney	Renin release	β1	–	–
Exocrine Glands			Secretion	–

Table 6. Types of Action of Representative Agents at Peripheral Cholingeric and Adrenergic Synapses and Neuroeffector Junctions

Mechanism of Actions	System	Agents	Effect
1. Interference with synthesis of transmitter	Cholinergic	Hemicholinium	Block of choline uptake, consequent depletion of acetylcholine (ACh)
	Adrenergic	α-Methyltyrosine	Depletion of narepinepherine (NE)
2. Metabolic transformation by same pathway as precursor of transmitter	Adrenergic	Methyldopa	Displacement of NE by false transmitter (α-methylnorepinephrine)
3. Blockade of transport system of membrane of nerve terminal	Adrenergic	Cocaine, imipramine	Accumulation of NE at receptors
4. Blockade of transport system of storage granule membrane	Adrenergic	Reserpine	Depletion of NE (MAO)
5. Displacement of transmitter from axonal terminal	Cholinergic	Black widow spider venom	Cholinomimetic followed by anticholinergic
	Adrenergic	Amphetamine, tyramine	Sympathomimetic
6. Prevention of release of transmitter	Cholinergic	Botulinus toxin	Anticholinergic
	Adrenergic	Guanethidine	Antiadrenergic
7. Mimicry of transmitter at postsynaptic receptor	Cholinergic		
	Muscarinic	Methacholine	Cholinomimetic
		Nicotine	Cholinomimetic
	Adrenergic		
	Alpha1	Phenylephrine	Sympathomimetic
	Alpha2	Clonidine	Sympathomimetic (periphery) Reduced sympathetic outflow (CNS)
	Beta1,2	Isoproterenol	Nonselective β-sympathomimetic
	Beta1	Dabutamine	Selective cardiac stimulation
	Beta2	Salbutamol	Selective inhibition of smooth muscle contraction
8. Blockade of endogenous transmitter at postsynaptic receptor	Cholinergic		
	Muscarinic	Atropine	Muscarinic blockade
	Nicotinic, N_M	Tubocurarine	Neuromuscular blockade
	Nicotinic, N_N	Trimethaphan, Hexamethonium	Ganglionic blockade
	Adrenergic		
	Alpha	Prazosin	α-Adrenergic blockade
	Beta1,2	Propranolol	β-Adrenergic blockade
	Beta1	Metoprolol	Selective adrenergic blockade (cardiac)
9. Inhibition of enzymatic breakdown transmitter	Cholinergic	Anti-ChE agents (physostigmine)	Cholinomimetic
	Adrenergic	MAO inhibitors	Little direct effect on NE or sympathetic response

DRUGS THAT REQUIRE THERAPEUTIC DRUG MONITORING (TDM)

- ❑ TDM is limited to drugs which demonstrate a good correlation serum concentrations and pharmacological response. TDM is often used for drugs that have a narrow therapeutic index (TI).
- ❑ Note: most drug concentration samples are taken as a trough (the lowest level before the next dose) Therefore sampling times are always immediately before the next dose.

PRINCIPLE: The goal of TDM is to individualize therapy through accurate dosage adjustments.

Abbreviations
- ❑ LD = Loading Dose
- ❑ MD = Maintenance Dose
- ❑ T1/2 = Half-Life

ANTIBIOTICS

Gentamicin and Tobramycin
- ❑ dosing
  - once daily dosing; 5mg/kg (expected peak 16 –20 mg/L, 18 hour post-dose concentration of <1 mg/L is desirable, since the drug has a 6 hour post antibiotic effect.
  - this regimen has been studied in stable, non-severely ill patients, but not in the extremes of age.
  - regular dosing: 1-2mg/kg, q8h, adjust for impaired renal function (peak 5-8 mg/L and trough < 2 mg/L)
  - time to peak: 15 minutes post 1 hour infusion
  - time to steady state (SS): 2.5 – 1.5 hours (7.5 – 75 hrs for > 30 years old)
  - T1/2 = 2 hours
  - elimination: renal
  - sample time: peak: 15 minutes post 1 hours infusion; trough: immediately prior to next dose

Increased concentration
Renal impairment
Nephrotoxic agents
- Cephalosporins
- Cyclosporine
- vancomycin
- amphotericin B

Decreased concentration
Increased clearance
- cystic fibrosis (CF)

Increased volume of distribution (3rd spacing)
- obesity
- severe congestive heart failure (CHF)
- ascites
- peritonitis
- burn patients

Vancomycin
- ❑ dosing: 1gm q12h over 1 hour to avoid "Red Man Syndrome"
  - time to peak: 60 minutes
  - time to steady state (SS): 20 –30 hours
  - sample time: peak: 1 hour post infusion; trough – immediately prior to next dose
  - therapeutic range: peak 25-35 mg/L
  - trough 5-10 mg/L
  - bioavailability: 100% IV, < 5% PO
  - T1/2: 4-8 hours, 6-10 days in renal impairment
  - elimination: renal: 80-90% unchanged

ANTICONVULSANTS

Phenytoin (Dilantin)
- ❑ LD
  - PO 15mg/kg divided in 3 doses administered at 2 hour intervals
  - IV 15-20mg/kg at <50mg/min (to minimize arrhythmias and hypotension)
- ❑ MD
  - 12 hours after loading dose
  - 300-400 mg or 5-7mg/kg once daily, titrate up to this dose can increase 30 – 100 mg/day every 10 – 14 days
- ❑ time to peak: 1.5 – 3 hours regular release, 3-9 hours for sustained release (SR)
- ❑ T1/2 = 8-40 hours
- ❑ time to steady state: 1-5 weeks
- ❑ therapeutic range: 40-80 mmol/L (correct for low albumin)
- ❑ elimination: 95% hepatic:
- ❑ protein bound (PB): 90%
- ❑ drug Interactions: numerous, many drugs decrease its metabolism (drugs metabolized by p450 drugs)

Concentration Correction with Low Albumin
- ❑ conc (µmol/L) = serum conc/(0.02 x albumin g/L) +0.1

Concentration Correction with Renal Failure
- ❑ conc (µmol/L) = serum conc /(0.01 x albumin g/L) + 0.1

Carbamazepine

❑ dosing: 1.6 – 1.8 g/day in 3 – 4 divided doses
- time to peak: 6-18 hours
- T1/2 = 10-25 hours
- time to SS: 2-4 weeks (naive patient); 2-6 days – prior carbamazepine therapy
- therapeutic range: 17-50 mmol/L
- elimination: 99% hepatic
- carbamazepine is an hepatic inducer, it induces the metabolism of most drugs and is a self inducer
- CNS side effects related to the concentration

PSYCHIATIRC MEDICATIONS

Lithium

❑ dosing: 600-1800 mg/day in 1 – 4 divided doses
- time to peak: 1-3 hours
- T1/2=18-20 hours (36 hours in the elderly)
- time to SS: 3-5 days
- therapeutic range: 0.6-1.0
- toxic effects with levels > 1.0 tremor, vomiting, slurred speech, confusion, seizure, coma
- adverse effects: nephrogenic diabetes insipidus

CARDIAC MEDICATION

Digoxin

❑ LD
- PO: 0.5 mg then 0.25 mg twice at 6 hour intervals
- IV: 0.01-0.02 mg/kg, give 50% of dose then 25% at 6 hour intervals

❑ MD
- 0.125 – 0.5 mg daily (CrCl >20mL/min)
- 0.125 mg daily if < 40 kg or elderly
- 0.0625 daily – 0.125 mg 3 times a week if CrCl < 20 mL/min

❑ time to peak: 60-90 minutes
❑ T1/2 = 40 hours
❑ time to SS = 5-7days
❑ therapeutic range: 1.0-1.9 nmol/L for CHF, 1.9-2.8 nmol/L for arrhythmias
❑ adverse effects GI: nausea, vomiting, diarrhea; CNS: headache, colour vision (yellow halos), confusion; cardiac: premature ventricular contractions (PVC), AV block, sinus bradycardia
❑ NOTE: TDM for digoxin is not routine, levels are only needed when a patient is symptomatic

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