Review of Pharmacology and Drug-herbs Interactions

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What is a drug?
What is a drug?

- A drug, broadly speaking, is any substance that, when absorbed into the body of a living organism, alters normal bodily function.

- Drugs are usually distinguished from endogenous biochemicals by being introduced from outside the organism.
What is a drug?

- The word Drug is derived from Middle Dutch meaning "dry barrels", referring to medicinal plants preserved in them.

- A medication or medicine is a drug taken to cure and/or ameliorate any symptom of an illness or medical condition, or may be used as preventive medicine that has future benefits.
Quiz

- Is advil a drug?
- Is Xiao Yao San a drug?
- Is Testosterone a drug?
Pharmacology vs. Pharmacy

- Pharmacology is from Greek pharmakon, "poison" in classic Greek; "drug" in modern Greek; and -logia "study of", "knowledge of"

- The branch of medicine and biology concerned with the study of drug action
What is Pharmacology?

- Pharmacology deals with how drugs interact within biological systems (e.g. organs like the heart or cells in GI tract) to affect function.

- It studies the reactions of the body and drug on each other.

- It also studies the sources of drugs, their nature, and their properties.
What is Pharmacy?

- It is the science concerned with application of the principles learned from pharmacology in its clinical settings.

- The primary contrast between the two are their distinctions between direct-patient care, for pharmacy practice, and the science-oriented field, driven by pharmacology.
Principles of Pharmacology

- It has become possible, through molecular analysis of receptors, to design chemicals that act on specific cellular signaling or metabolic pathways by affecting sites directly on cell-surface receptors.

- A receptor is a cell or group of cells that receive stimuli OR a molecule (such as a protein) on the cell surface or in the cell interior that has an affinity for a specific chemical group or molecule or a virus.
receptor
What is a metabolic pathway?

- In Biochemistry, metabolic pathways are series of chemical reactions occurring within a cell.

- A metabolic pathway involves the step-by-step modification of an initial molecule to form another product.
Example of metabolic pathway
Principle of pharmacology

- When describing the properties of a chemical (drug), pharmacologists are often interested in LADME
LADME

- Liberation (disintegration of solid drugs)
- Absorption (how is the drug absorbed)
- Distribution (how does it spread)
- **Metabolism** (Is the medication converted chemically inside the body, and into which substances. Are these active? Could they be toxic?)
- Excretion (how is eliminated)
Drug metabolism is the biochemical modification of pharmaceutical substances by living organisms, usually through specialized enzymatic systems.

Usually occur in the liver but can occur in other local tissues like the lung, intestine and Kidneys.
Drug metabolism often converts lipophilic (fat soluble) chemical compounds into more readily excreted polar (water soluble) products.

Its rate (the speed at which it occurs) is an important determinant of the duration and intensity of the pharmacological action of drugs.
Drug metabolism can result in **toxication** or **detoxication** - the activation or deactivation of the chemical.

While both occur, the major metabolites (products of metabolism) of most drugs are detoxication products.
Drugs are almost all xenobiotics (introduced from the outside the body).

Other commonly used organic chemicals (like herbs) are also xenobiotics, and are metabolized by the same enzymes as drugs. This provides the opportunity for drug-drug and drug-chemical interactions or reactions.
First Pass Metabolism:

Venous system: transmits blood from nose directly to the heart — no liver metabolism

Liver: 90% of oral medication is metabolized and destroyed by the liver before it gets to the heart.

Portal circulation: All blood from the intestines is taken to the liver for detoxification.

Nasal: Drug absorbs directly into the veins

Heart: pumps blood out to entire body — no delay

Oral medications: Sit in the stomach for 30-45 minutes
Quiz

- What are the principles of pharmacology?
- What is metabolism?
- What's the difference between polar and non-polar products?
- Why is it important to produce polar products?
What is a receptor?

- A receptor is a molecule most often found on the surface of a cell, which receives chemical signals originating externally from the cell. Through binding to a receptor, these signals direct a cell to do something.

- Receptors are protein molecules, embedded in either the plasma membrane (surface receptors) or the cytoplasm or nucleus (nuclear receptors) of a cell.
What is a Ligand?

- A molecule which binds (attaches) to a receptor is called a ligand, and may be a peptide (short protein) or other small molecule, such as a neurotransmitter, a hormone, a pharmaceutical drug, or a toxin.

- *Not every* ligand that binds to a receptor also activates the receptor
Types of ligands

- **Full agonists** are able to activate the receptor and result in a maximal biological response. The natural endogenous ligand with the greatest efficacy for a given receptor is by definition a full agonist (100% efficacy).

- **Partial agonists** do not activate receptors thoroughly, causing responses which are partial compared to those of full agonists (efficacy between 0 and 100%).
Antagonists bind to receptors but do not activate them. This results in receptor blockage, inhibiting the binding of agonists and causing the opposite effect to what the agonist normally produces in the cell.
Ligand

Ligand binding domain on external surface of cell

Plasma Membrane

Transmembrane portion of receptor

Signal transduction domain of receptor exposed to cytoplasm

Signal Transducer
Receptor Site Interactions

- Neurotransmitter
  - Receptor site
  - Neurotransmitter
  - Gives pharmacological response

- Agonist
  - Receptor site
  - Agonist
  - Gives pharmacological response

- Antagonist
  - Receptor site
  - Antagonist
  - Gives no pharmacological response

C. Ophardt et al., 2003
Quiz

● What is a receptor?

● What’s the difference between a full agonist, partial agonist and antagonist?

● Does an antagonist illicit a biological response?

● Define transduction.
What is the half life of a drug?

- A **biological half-life** or **elimination half-life** is the time it takes for a substance (drug, hormone, neurotransmitter or other) to lose half of its pharmacologic, or physiologic activity.

- It can also mean the time it takes for the **blood plasma** concentration of a substance to halve ("plasma half-life") its steady-state.
What is the Therapeutic Index?

- Medication is said to have a narrow or wide therapeutic index or therapeutic window.

- This describes the ratio of desired effect to toxic effect.
● A compound with a narrow therapeutic index (close to one) exerts its desired effect at a dose close to its toxic dose.

● A compound with a wide therapeutic index (greater than five) exerts its desired effect at a dose substantially below its toxic dose.
Those with a narrow margin are more difficult to dose and administer, and may require therapeutic drug monitoring.

For example, most anti-cancer drugs have a narrow therapeutic margin: toxic side-effects are almost always encountered at doses used to kill tumors.
Quiz

- Give an example of a drug/herb that has a wide therapeutic index.
- Give an example of a drug/herb that has a short therapeutic index.
- What is half-life?
What is pain?

- **Pain** is an unpleasant feeling often caused by intense or damaging stimuli.

- The International Association for the Study of Pain's widely used definition states, "Pain is an *unpleasant sensory and emotional* experience associated with *actual or potential* tissue damage."
Pain is the most common reason for physician consultation in the United States.

It is a major symptom in many medical conditions, and can significantly interfere with a person's quality of life and general functioning.
The Pain Cycle involves several factors:

- Anger, Frustration & Helplessness
- Loss of Normal Function
- Muscle Weakness
- Restricted Mobility
- Muscle Spasm & Inflammation
- Guarding

These factors create a cycle that perpetuates pain and its consequences.
Causes of pain

- Inflammatory (usually from physical trauma)
- Mechanical
- Neurological
- Central/global/sensitization
- Psychosocial
- Auto-immune (usually inflammatory minus trauma)
Quiz

- Define pain
- Give an example of each of the usual causes of pain
NSAIDS

- Mostly used for nerve root pain and/or Joint inflammation.
- Examples include: Advil, Aleve, Naprosyn, Relafen, Voltaren, Celbrex.
NSAIDS

- Block Cyclooxygenase (COX) enzyme hence blocking prostaglandin synthesis.

- Celebrex and Vioxx are more specific and block COX-2 enzyme causing less side effects than earlier generation NSAIDS.
Inflammation & pain

- Macrophage (Phagocyte)
- Histamine Heparin etc.
- Mast cell
- Phospholipids
- Phospholipase
- Corticosteroids
- Interleukin 1-β, 8 & TNF-α (Cytokine)
- Immunoglobulin (Antibody)
- Arachidonic acid
- Cyclooxygenase 1 & 2
- CoX-inhibitors NSAIDs ASA
- Lipoxygenase
- Leukotrienes
- Prostaglandins (PGE2)
- Thromboxane

- T lymphocyte (T-cells)
- B-lymphocyte (B-cells)

- TH3
- TH1
- TH2

- TGF-β (Cytokine)

- Traumeel

- Pro-inflammatory

- Traumeel
NSAIDS

- Most common side effects:
  - GI (inhibits PGG which protects gastric mucosa)
  - Hepatic
  - Renal Insufficiency
  - Increase Blood Pressure
  - Bronchospasm (asthma)
  - Rash, Urticaria
  - Stroke and CAD
Quiz

● At what part of the inflammatory cascade do fish oils like EPA and DHA work?

● What is the first manufactured pharmaceutical drug in history?
Steroids

- Medrol dose pack (high to low dose taper)
- Blocks release of AA
- SE include behavior and mood alteration, fluid retention, HTN, glucose intolerance, osteoporosis, adrenal atrophy, myopathies.
Oral Steroids

MethylPREDNISolone TABLETS, USP 4 mg

Qualitest®
Epidural steroid injection

- More useful for sciatica than localized BP.
- Combo of steroids which starts working in 3-10 days and local anesthetic lasting for only 2-3 days.
- Performed under sterile conditions with guided fluoroscopic X-ray.
Epidural steroid injection
The steroid medication is injected into the epidural space.

Dura
Subdural space containing spinal fluid

Fig. 1

Epidural space
Spinal cord
Cross-section of vertebrae
Steroid SE

- Facial flushing, rash, insomnia, emotional, lightheadedness caused by anesthesia.
- Temporary flare up in 5% of patients caused by the steroid.
- Allergic reaction to X-Ray dye.
- Bleeding, infection and/or nerve injury due to puncture.
Quiz

- What is the difference between NSAIDS and Steroids?
- What are the most common SE of NSAIDS?
- What are the most common SE of Steroids?
Non inflammatory pain medication
Tylenol (paracetamol)

- Blocks Prostaglandin centrally
- Limit to 2-4 grams/day
- Used in combo with Opiates
- Side effects are mostly limited to Liver
Narcotics (special prescription)

- Includes Darvocet, Ultram, Vicoden, Percocet, Oxycontin, Dilaudid.

- Block pain in the central nervous system (they have no anti-inflammatory property)

- SE are related to the CNS and include respiratory depression, constipation and a high addictive potential.
Side effects of Oxycodone

Central:
- Hallucination
- Confusion
- Fainting
- Dizziness
- Loss of appetite
- Lightheadedness
- Drowsiness
- Headache
- Mood changes

Skin:
- Hives
- Rash
- Flushing
- Sweating
- Itching

Mouth, tongue or lips:
- Swelling
- Dryness

Face:
- Swelling

Eyes:
- Swelling
- Smaller pupil
- Redness

Throat:
- Hoarseness
- Swelling
- Difficulty swallowing

Heart:
- Fast or slow heartbeat

Muscular:
- Seizures
- Weakness

Gastric:
- Nausea
- Vomiting

Hands, feet, ankles, or lower legs: - Swelling
The PURSUIT of HAPPINESS
Neurological pain killers
Antidepressants

- Act on pain by inhibiting presynaptic reuptake of certain neurotransmitters like NE, Serotonin and DA.

- Mostly used for chronic pain and peripheral neuropathies.
Antidepressants

- Common SE:
  - Sedation, insomnia
  - Orthostasis
  - Anticholinergic SE such as blurry vision, dry mouth, tachycardia, constipation, urinary retention, and memory dysfunction.
Anticonvulsants

- Mechanism of Action is very similar to antidepressants
- Most commonly used one is Neurontin (gabapentin)
  - inhibits the GABA neurotransmitter in the brain hence decreasing neuron firing
  - SE include somnolence, dizziness, and ataxia.
Quiz

- List some commonly used non-inflammatory pain killers

- List the mechanism of action of each of the above.
Anti-Coagulants (non-pain meds)
Warfarin (Coumadin)

- Inhibits vitamin-K dependent coagulation factor synthesis.
- Metabolized in Liver
- High potential for drug, herb and food interaction (green tee, cruciferous vegetables, grapefruit)
- SE include high bleeding potential, GI, headaches, fatigue and fever
Heparin

- Anti-coagulation mediated by inhibition (binding) to anti-thrombin III and destroying thrombin clotting factors.
- High potential for drug interaction including Ginseng, Ginko, green tea, horse chestnut, goldenseal, ginger, garlic and flax seed.
- Major side effect is bleeding
Plavix (clopidogrel)

- Reduces platelet aggregation and activation
- Metabolized in the liver
- SE include GI, general bleeding, dizziness, fatigue, Headaches, and palpitations.
Quiz

- What's the difference between the three types of anti-coagulants?

- When are each of the above used?
Pain according to TCM

- Qi and blood Stagnation
- Blood stasis
- Bi-syndrome
- Blood and/or qi deficiency
- Exterior wind related pain
- Blood Heat
- Interior cold
Heat Clearing and blood cooling
Sheng Di Huang (radix Rehmanniae)

- Has Anti-inflammatory effects
- Improves endocrine function
- Hemostatic, diuretic, and anti-hypertensive
- Use with caution in patients on anti-coagulants and blood pressure meds.
Mu Dan Pi (cortex Moutan)

- Anti-inflammatory and sedative
- Improves cardiovascular function
- Anti-hypertensive
- Use with caution in conjunction with anticoagulants.
Blood invigorating herbs

- General caution or contra-indication is with Anti-coagulants and anti-platelet agents.

- This Caution includes most herbs in this category including Tao Ren, and Yi Mu Cao
Chuan Xiong (Rhizoma Ligustici)

- Has anti-coagulant and anti-platelet properties
- Sedative and muscle relaxant
- Improves cardio-vascular function
- Use with caution or don’t use in patients taking Plavix, heparin and/or warfarin
Yan Hu Suo (Rhizoma Corydalis)

- Anti-inflammation
- CNS sedative
- Muscle relaxant
- Use with caution in patients taking narcotic analgesics.
Jiang Huang/E Zhu (curcumin)

- Anti-Inflammatory
- Good results in arthritis studies
- Good results as anti-cholesterol agent
- Anti-platelet
- Do not use with Warfarin and Heparin
- Caution in patients on aspirin and/or Plavix
Dan Shen (Radix Salviae)

- Anti-coagulant, Cardio-protective, anti-platelet, Hepato-protective, sedative
- Do not use with Warfarin and Heparin especially if combined with other blood moving herbs
- Do NOT use with Digoxin (digitalis) since it falsely alters free Digoxin levels in the blood.
Zelanium (herba Lycopii)

- Good for pain and bruising.
- Cardio-tonic
- Has diuretic effect.
- Use with caution if patients is taking other pharma diuretics such as Furosemide (lasix), or hydrochlorothiazide.
Blood tonifying herbs
Dang Gui

- Anti-inflammatory and Analgesic
- Anti-platelet
- Good for Uterine muscles and function
- Caution with anti-coagulants and anti-platelet
- Studies have shown that Dang Gui protects the liver from Acetaminophen (tylenol) induced toxicity.
Bai Shao

- Has multiple positive effects on both smooth and skeletal muscles.
- Analgesic and sedative
- Caution with other sedatives like Benadryl, Benzodiazepin (Xanax) and opiates.
- Caution in diabetics since it lowers blood glucose increasing potential for hypoglycemia
Da Huang (purgative)

- Good anti-biotic and anti-viral (heat)
- Good for GI
- Good for Kidney (western)
- Use with caution with cardiac glycosides such as Digoxin since it affects potassium levels in blood
Wind-Damp dispelling herbs
Du huo (Radix Angelicae Pubescentis)

- Analgesic and anti-inflammatory
- Anti-biotic
- Anti-platelet
- Use with caution with other anti-coagulants and anti-platelet such as aspirin and warfarin.
Qin Jiao

- Anti-inflammatory
- Sedative
- Increases blood glucose level
- Use with caution with other sedatives
- Use with caution with diabetic patients
Wind-Heat releasing herbs
Ge Gen/Kudzu (radix Puerariae)

- Anti-diabetic
- Anti-platelet
- Anti-spasmodic
- Use with caution in patients on anti-coagulants
- Use with caution in diabetic patients on other drugs.
Chai Hu

- Anti-viral
- Good for liver damage
- Common cold
- Has been determined to interfere with ofloxacin (anti-biotic), tolbutamide (anti-diabetic) and interferon (anti-viral)
Interior warming herbs
Fu Zi (Radix Aconiti)

- Improves cardiac function
- Good anti-inflammatory
- Can be toxic (TE smaller than other similar herbs) so use with caution
- Interacts with other cardio-tonics like Dogxin and Anti-arrhythmic medication like B-blockers and quinidine.
Qi Tonics
Gan Cao (radix Glycyrrhizae)

- Anti-inflammatory
- Intestinal spasms
- Ulcer
- Endocrine tonic
- Use with caution along Steroids since it has been shown to increase their half life
- Use with caution with diuretics (lasix) and cardiac tonics (digoxin)
Ren Shen

- Many positive effects on the nervous, endocrine, immune, and reproductive systems.
- Reduces blood sugar levels so use with caution in diabetics.
- Use with caution in patients taking anti-depressants and stimulants since there are some reports suggesting that Ren Shen induced Mania in those patients.
Bai Zhu

- Adaptogenic and immuno-stimulant
- Anti-platelet
- Diuretic
- Enhances the effects of Omeprazol, a proton pump inhibitor given for peptic ulcers
- Use with caution in patients taking diuretics (lasix, hydrochlorothiazide) and anti-platelets and anti-coagulants.
“What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?”
References

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