**Topic 2: Pain. Jan 14th 2019**

Pain medication

- 1)Prescription drugs
    - 300 billion per year (US) + requires doctors prescription
- 2)Over the counter (OTC)
    - $25 billion per year
    - No prescription needed
    - Some are “behind the counter”

Top OTC meds (NA 2016)

- cough/cold 8.2 billion , Pain reliever 4.1 bill ,Antacid - 2.7 bill, Toothpaste - 1.5 bill , Laxative - 1.3 bill

Important considerations when buying:

1. **Safety**: dose makes the drug + makes the poison
   Side Effects (All drugs have side effects )
    - Effect- what is it? : info easy to find, label or box, google
    - Incidence- how common is it (that side effect occurs)? : info is difficult to find
    - Need both to evaluate risk
2. **Indications**: What to use for? Many people take the wrong drug, Many people take drugs unnecessarily
3. **Counter Indications**: When you should NOT use . Conditions , foods, “natural” remedies (supplements)

Pain relievers most common OTC drug

- 4.1 billion/year (NA) ,50 billion tablets, (NA) 1600 tonnes/year ,500 dump trunks

**Asprin-** World most popular drugs : alcohol, caffeine, aspirin, nicotine

- *Salix* (Genus family): willow, poplar, beech, wintergreen
- Salicylates:
    - Sumerians used willow leaves for pain 2,200 BC
    - Egyptians used willow for inflammation
    - Knowledge of herbs lost in the dark ages: a lot of the information go away

Reverend Edward Stone 1702-1768 (helped discover salicin NOT aspirin)

- Rector in church of England, Described treatment for ague in 1763
- Willow bark has a bitter taste : similar to quinine
- Doctrine of Signatures
- Association between disease and cure
    - People who live near swamps get malaria
    - People with malaria have fever
    - Treat malaria with quinine
    - Quinine is bitter
    - Willow bark is bitter
    - Willow grows in swamps
    - Willow bark will cure for fever

Willow bark for fever

- Dried bark, ground to powder and given for fever
- Expensive, limited supply, variable effectiveness

Active ingredient in willow is salicin (NOT ASPRIN), isolated in 1829

- A little Salicin from A LOT of bark (therefore only rich people can consume this)

Salicylic Acid : Salicin converted to salicylic acid in 1838 (occurs in the BODY)

- Better drug than salicin (lower dosages)
- Occurs in meadowsweet flowers (very small amounts)
- Analgesic (reduces pain) , Antipyretic (reduce fever), Anti Inflammatory (reduce swelling)
- Better product than original salicin + more effective on lower doses, and more widely available to the general public!
- Salicylic Acid manufacture from car toal (oil) : lower the price, and available in larger quantities
- 1800's Coal tar was a waste product, take coal and convert to coal gas, and tar waste oil (petroleum)
- (to light street lamps)

Synthetic Vs Natural : The outcome is IDENTICAL

- Natural ( from plant/animal/ rock)
    - 58 billion tablets require 2 million tonnes of bark) = salicylic acid
    - Issue is the SUPPLY
- Synthetic (how we make it -material manufacture from OIL/coal)
    - use coal tar, 58 billion tablet require 62 000 tonnes of oil - (Kolbe Schmitt reaction) = Sal' acid
    - Advantages: manufacture much larger quantities for a much lower price

Dye companies specialized in coal tar chemistry: make large quantities at a low price+ open up drugs to more people

Salicylic acid was a drug with problems

- Benefits : Analgesic, Antipyretic, Anti Inflammatory
- Side effects: Bitter taste, stomach irritation (can KILL you)

Felix Hoffman 1869-1946 (father had arthritis)

- Took salicylic acid for pain
- Suffered from stomach problems
- Trial 1) Problem of drug optimization: Salicylic acid (made small changes to molecular structure), and made something else : taste less bitter, no stomach irritation, BUT not effective for pain

- August 10, 1897: Salicylic acid > Acetylsalicylic acid (first artificial drug)
    - Artificial : something designed created by humans, does not occur in nature , purely synthetic
    - Aspirin was manufactured from coal tar/petroleum

Aspirin initially sold as a powder

- Aspirin tablets became more popular (take off bitter taste, and standardize the dose: take 1 tbsp they can have different spoon size etc)
- Aspirin (trade name ) and A.S.A Acetylsalicylic acid (generic name/ scientific name)
-

A.S.A Benefits

1.Pain

- Good for muscular pain (outer part of body)
- Not effective for visceral pain (inner part /organs of body)
- Interfere with production of prostaglandins (local hormones)
    - Produced and "used" in the same cell + exist for short times in the body
    - Prostaglandins causes you to feel pain !

- Arachidonic acid -cyclooxygenase (enzyme) to convert that > prostaglandin
- Aspirin blocks the cyclooxygenase machine, so less prostaglandin made and that makes you feel less pain

2. Antipyretic - (Reduce fever) + inflammation ( anti-inflammatory)
3. Reduce heart attack risk
   - One Aspirin tablet for every 2 days for 5 years
   - Only if doctor says in high risk pop

A.S.A and cancer? - long- term use of aspirin and risk of colorectal cancer

Side effects: tinnitus, stomach irritation,blood clotting
- Aspirin is used to make explosives
- Death : >60 tablets at once

Tinnitus: ringing sound in your ears, More than 10 tablets, Warning of salicylism (aspirin poisoning)
Stomach irritation (Long term use)
- Excess HCl cause corrosion to stomach, mucus protect stomach from damage of HCL
- Prostaglandins help to protect the stomach
  - Decrease acid production + increase mucus production = more protection
- Note: Arachidonic acid - cyclooxygenase (enzyme) to convert that ( Aspirin blocks enzyme from working) > prostaglandin
  - No prostaglandin = no mucus + more acid production = will cause stomach damage (long term use)
- Bufferin: Contains an antacid – $MgSO_4$ (gypsum) + Pills dissolve quickly
- Plastic coating on A.S.A
- Avoid irritation of the stomach

Reye Syndrome and influenza
- Found in children
- Children's aspirin no longer available
- No causative link between ASA and Reye syndrome
- Children's Aspirin removed as a precaution

Cause vs Association
- Association between 2 things does not mean that one thing is influenced (caused) the other
- Cause: requires a body of evidence
  - Association between two things
  - Control experiments :eliminates other possibilities
  - Experiments with animals
  - Biochemical explanation of the effect
  - Deliberately change one factor to look for changes in the other

Cause: Aspirin and stomach irritation ( An example from above)
- Ulcers common in people who take Aspirin (long term)
- Ulcers less common in people who don't use Aspirin (control)
- Aspirin dosing in rats results in more ulcers (animal)
- Prostaglandin production in stomach lowers stomach acid and increases mucus production (biochemical)

- Aspirin use raises stomach acid and decreases mucus production bc Aspirin inhibits prostaglandin production
- Stomach irritation reduction if stop taking Aspirin (change)

Myths/ Additive info

- Regular/Extra strength
- Tablet vs caplets vs gel caps : all are effective
- Some forms add caffeine for headaches : A.S.A. 325 mg , Caffeine 32 mg
- Name brand vs Generic (same quality as name brand):
  - Quality cost more , people think name brands and quality (yes for laptop/clothing )
  - **But not for chemical substance**
  - Same chemical substance (water is water) ,Same dosage ,Equivalent bioavailability – Same amount of drug enters the body
  - Use name brand to find the generic

Price per 100 tablets

- Bayer aspirin low dose is 8 times the price of bayer aspirin (general)
- Generic A.S.A - 2.5 $

***History of Acetaminophen***

A .Cahn and P Hepp 1866

- Experimenting to find a vermifuge
- Noticed fever reduction in person who was given acetanilide

Antikamnia (antifebrin)

- Made from coal tar
- Discovered by accident

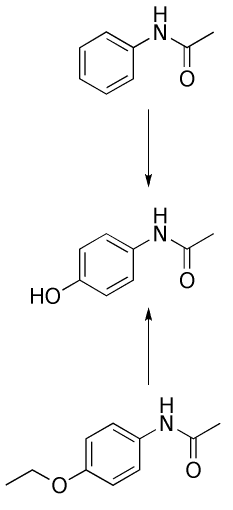
Carl Duisberg (chemist at Bayer): needed to dispose 50 tons of aminophenol , discovered Phenacetin

- He didnt sell until 30 years later because ht thought it would be too toxis

Phenacetin - APC tablet (Aspirin, Phenacetin, Caffeine)

Both drugs converted to acetaminophen in body - 1947

Antikamnia > Acetaminophen (pain relieving) < phenacetin (diagram in order)




Acetaminophen (Tylenol)

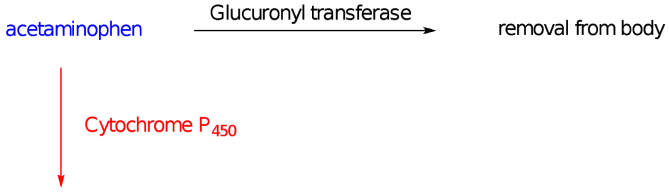
- For pain relief by raising pain threshold (reduce body ability to feel pain)
- For muscle pain and visceral pain (organs)
- Helps with reducing fever (antipyretic)
- Not for inflammation: does not inhibit prostaglandin synthesis

Arthritis use- variable effectiveness

- Osteoarthritis
- Not good for : Rheumatoid arthritis (involves inflammation ) therefore you need something with prostaglandin

Side Effect (Acetaminophen)

- Stomach Irritation
  - A.S.A: strong irritation (chronic)
  - Acetaminophen : weak irritation



- Death : more than 60 tablets, #1 suicide drug in England
- Liver Toxicity :liver metabolises things, chemically change compound to something else to remove in the body

    - Safe: Acetaminophen > (Glucuronyl transferase enzyme) removal of from body
    - Bad: Acetaminophen > (cytochrome P 450) **toxic metabolite** > liver damage (too much)
        - Naturally it creates a bit of this toxic metabolite so if u take a lot then not good because it will metabolise  accumulate = damage

- **Never take acetaminophen for hangover: **alcohol stimulates liver function (by activating red path)**
- Acetaminophen poisoning is very common
- Acetaminophen is in many prescription meds and OTC meds

No risk of Rye syndrome- no association for acetaminophen

- Children's tylenol in small bottles
- Make it in liquid form so that they can take it, and specialy formulated for different metabolism of the hild

Drug Dosages:

- Tylenol Regular : Acetaminophen 325 mg
- Tylenol extra strength : 500g
- Arthritis of muscle/body: 650mg
- Tylenol migraine : Acetaminophen 500mg, caffeine 65mg

Tylenol and cyanide - 1982

- Took many tylenol bottles, opened it (capsules), took out the acetaminophen, then put cyanide and put the bottle back into the drug store
- Tylenol was recalled by J&J in every single capsule world wide
- Tylenol caplets replace capsules (think of chalk seal )
    - And you can get capsules but it is prescription
    - Safety seal added to all OTC meds (tamper proof)

Summary of Acetaminophen

| Benefits | Side Effects |
|---|---|
| Y: Pain, fever<br>N: inflammation ,prevent heart attack | Y: liver toxicity<br>N: Reduced blood clotting, stomach irritation, Rye syndrome |

Price for 100 tablets

- Children's tylenol: the most expensive 32.99(but worth for the safety)
- Tylenol migraine more expensive but you can save $ by just having your own caffeine
-

***Ibuprofen (Advil)***

- Developed in 1961
- Originally prescription only
- Otc approved use 1984
- Inhibits cyclooxygenase: blocks the active site ( like aspirin)

| Benefits | Side Effects |
|---|---|
| - Pain, fever, inflammation<br>- (doesn't help with heart attack) | - Reduced blood clotting, stomach irritation<br>- Rye syndrome (no), liver toxicity (no) |

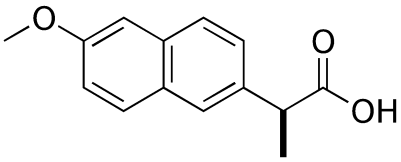
Ibuprofen: 200mg

- Motrin and advil are the same stuff
- Read the back of the box and NOT THE front
- Advil migraine ( 200 mg ibuprofen) and Regular advil (200 mg ibuprofen) but you pay more for migraine label

Price for 100 tablets : add the charts in later

- Advil migraine - you pay 50% more
- Motrin is cheaper ( but identical)
- Children's is more expensive

***Naproxen (Aleve)***




- Very good for inflammation
- Generic now available
- Relatively expensive

Top Pain relievers (NA)

- Acetaminophen 43%, A.S.A 28%, Ibuprofen 26% , Naproxen 3%

| Effect | A.S.A | Acetaminophen | Ibuprofen | Naproxen |
|---|---|---|---|---|
| Pain | Y | Y | Y | Y |
| Fever | Y | Y | Y | Y |
| Inflammation | Y | N (no prostaglan' | Y | Y |
| Prevent Heart Att | Y | N | n | n |
| Redc blood clotting | Y | N | Y | Y |
| Stomach Irritation | Y | N | Y | Y |
| Rye Syndrome | Maybe | N | N | N |
| Liver Toxicity | N | Y | N | N |

***COX1 and COX2 + Arthritis***

Effect of COX-1 Inhibition (Harmful Effects)

- Stomach :HCL production increases + Mucus production decreases
- Platelets : clotting is inhibited
- Long term COX-1 inhibition: ulcers in stomach can bleed severely

Effect of COX 2 inhibition :Reduces pain, inflammation, fever = beneficial

Current arthritis treatments

- Inhibit both COX1, and COX2

- COX-2 is **beneficial**: reduce pain, reduce inflammation
- COX-1 is **harmful** – Stomach irritation – Blood clotting inhibited – Bleeding ulcers in chronic users

Selective COX-2 inhibitor for arthritis (vioxx)

**Vioxx Clinical Trials (Arthritis drug)**

- Approximately 60 studies were done
- More than 5000 patients
- No serious side effects
- No difference in cardiovascular disease vs placebo
- Drug approved in 1999: sales avg 2.5 bill/year

VIGOR- **VI**OXX **G**I **O**utcomes **R**esearch : was done for marketing

- Illustrate reduced risk of ulcer
    - 18 month study
    - Used naproxen as a placebo
        - Used VIOXX at twice the normal dose
        - Naproxen was given at the normal amount
- Study showed 54% reduction in serious GI side effects with VIOXX
    - 56 out of 4047 for VIOXX
    - 121 out of 4029 for naproxen

Full VIGOR data released to FDA

Increases risk of Heart Attack

- 0.4% for VIOXX (45/4047 patients)
- 0.1% for naproxen (19/4029)
- No difference in mortality

Paper in NEJM reported no adverse effects : only data from first 10 months was included

Media went crazy on VIOXX

FDA analysis of 1.4 million patients

- Estimated that VIOXX caused 88,000- 139,000 heart attacks during 1999-2004
- In 2004 , Merck voluntarily removed drug from market: cut 7000 jobs, >10,000 lawsuits

2005 Advisory Panel Conclusions

- They thought drug should be put back into the market
- The benefits outweigh risk

Benefits outweigh risks

- Current Arthritis treatment
    - FDA estimates 10,000- 20,000 deaths/year from gastrointestinal bleeding
- VIOXX as an arthritis treatment
    - FDA estimates 18000-28000 heart attacks/year
    - Risk of heart attack similar to ibuprofen
    - Improved labelling and MD education
- Merck refused to re-introduce the drug: risks outweigh benefits ,> 10 000 lawsuits