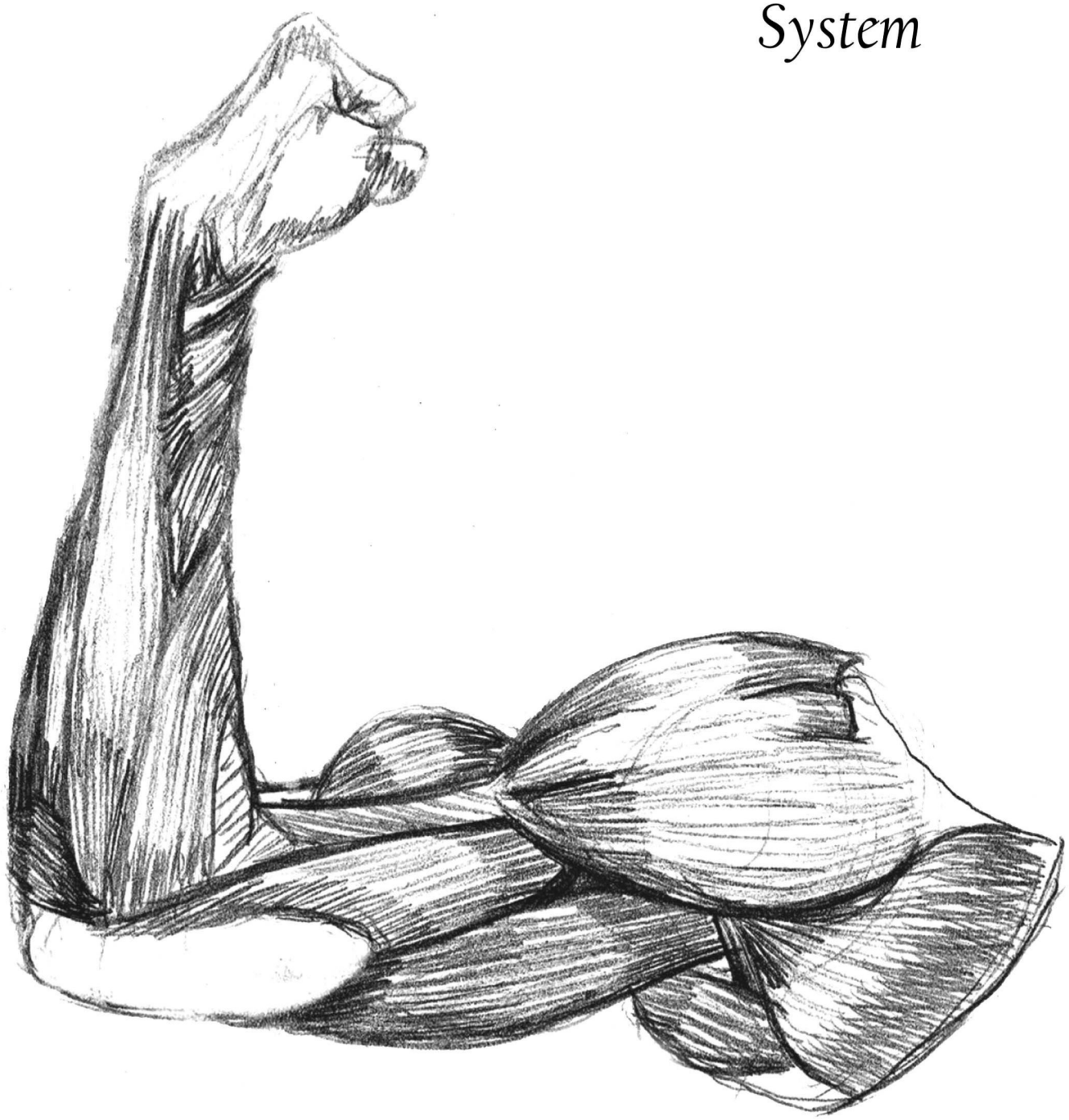
Medical Committee
The University of Jordan

The Skin and MUSCULOSKELETAL System



PHARMACOLOGY

SLIDES ☐
SHEET ■
LECTURE # 5

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Acetaminophen (Paracetamol)

This drug's trade name is Panadol which is known amongst people. (actually the doctor said that Panadol is the generic name which is not true)

It is effective centrally (on the CNS) -mostly in the brain- , having an effective treatment as an analgesic and an antipyretic. It is not effective as any other treatment in the peripheral tissues. Since it is a prostaglandin inhibitor, why does its inhibition work in the CNS but not in tissues?

Some say it's unknown, others claim that: Prostaglandins receptors in the hypothalamus (thermostat) and spinal cord belong to a different group than COX1 and COX2, probably to COX3

Henceforward it is not prescribed in case of rheumatoid arthritis. (which is mainly in peripheral tissues such as joints)

Pharmacokinetics:

1) available as tablets , administered orally and possible in most patients.

Absorption is rapid and almost complete.

2) available as suppositories , to be administered rectally in case of children, unconscious or vomiting patients.

3)The book mentions that the drug is also available as intravenous formulaion.*

After absorption and before reaching the circulation/blood, significant part is removed through first-pass effect, which is caused mainly by metabolism in the luminal cells of GI tract and liver, so NOT all the administered dose reaches systemic circulation and produces an effect

Metabolism

Eliminated mainly by the liver, (hepatic metabolism) specifically in hepatocytes, in particular on the ribosomes of the ER by Cytochrome P450

We have two phases of metabolism, phase 1 (oxidation) and phase 2 (conjugation). Drugs may go through phase I or phase 2 or both.

Regarding this drug, it firstly gets oxidized, forming a metabolite called N-acetyl-p-benzoquinoneimine NAPQI (highly toxic intermediate). NAPQI has to go through rapid detoxification which takes place in phase 2 by conjugating it (NAPQI with glutathione (via enzymes in the liver).

This intermediate toxic substance (NAPQI) means that the metabolism of this drug (Paracetamol) goes into two phases; the first one is oxidation which results in a toxic intermediate substance that is rapidly detoxified by conjugation reactions (ex. glucuronidation, sulfoxidation or mainly with glutathione) to become non-toxic. If this substance (NAPQI) accumulates in hepatocytes, it will react with sulfhydryl groups of proteins and enzymes, resulting in hepatocyte necrosis and toxicity.

This process is referred to as *sequential*, as the drug needs to pass through phase 1 first before being converted to a safe non-toxic compound. This makes this drug unsafe if the dosage is increased since it may result in acute hepatitis and death.

Excretion of the drug and its metabolites is done through urine.

Therapeutic uses: only 2

1)Antipyretic, for example during inflammation of the tonsils (tonsillitis) the body temperature increases from to 38, the drug is then prescribed in order to reset the thermostat in the hypothalamus back to normal (37 degrees).

2) Analgesic: pain (integumental pain, tooth ache, sciatica, mild pain, and headache possibly even though it belongs to a different category. Not used in bone fracture or cancer for example, it is of no benefit in deep pain.

Many students keep asking about **aspirin**, why is it not preferred in children?

It can cause **Reye's syndrome** which occurs most likely in children, especially when they have a **viral infection** (ex. Chickenpox), it is **contraindicated**, the fatal consequences are over 50%.

Panadol is used as an alternative therapy, and the drug of choice in children.

Actually you can use aspirin as antipyretic or analgesic in children but you have to check first that there is no viral infection, which is difficult sometimes to be differentiated from bacterial infection, so use Panadol at first.

A small dose of aspirin can be used with patients of gout with high uric acid (acute attack of gout), however when using acetaminophen, the therapeutic dose can be given safely without any problems.

For patients with uricosuric agents drugs like Probenecid, Sulfinpyrazone, aspirin is absolutely contraindicated, so acetaminophen is given instead. Also to patients with gastric or peptic ulcers (where aspirin cant be given)

Adverse effects:

Fortunately, in the case of the therapeutic dose, there are almost no side effects, (very few, almost non existing) however there could always be an allergic reaction in a particular group of patients, and leukocyte effects (i.e. change in leukocyte count). These side effects are transited (reversible) if you stop taking the drug.

The problem occurs when large doses are given over a long period of time (regular treatment), there would be a risk of kidney damage, renal tubular necrosis, or hypoglycemic coma. Those are most significant in elderly (old patients). So, acute renal failure is one of the side effects which results from chronic use, but the most common is hepatic faluire.

Most commonly, toxicity occurs during accidentally/suicidal attempts: what happens is that the amount of glutathione that detoxifies NAPQI is limited, when a large dose is administered, oxidation MUST happen (because it is sequential) so there will always be metabolites, then depletion of glutathione storages occurs and there will be an accumulation of N-acetyl-p-benzoquinone imine in the liver hepatocytes, causing liver necrosis and death. So the rate limiting factor is glutathione and conjugation not oxidation .

How do we treat toxicity?

Immediate treatment: induce vomit in the patient, then take him/her to the hospital where they are treated by gastric lavage and active charcoal, and by giving the patient glutathione (oral) or n-acetylcysteine (intravenous).

How much exactly is the large does?

Relatively speaking, it is 2-3 times more than the therapeutic dosage.

Theoretically speaking, we can give cyt p450 inhibitors, it efficiently inhibits COX in rats, but practically, that won't work in humans, it could only be used as a prophylactic. (this is not mentioned in books because it has no *clinical* value, it is related to experiments)

Immediate treatment is needed to prevent formation

Why do we need to respond quickly to the toxicity of the patient?

To prevent formation of covalent (irreversible bonds) between enzymes and their receptors.

Sometimes, the glutathione storage in the body can affect normal dosage causing toxicity, for example, if a woman was on a strict diet, she would have low glutathione amount in her body, so if she took normal dosage of Panadol, there may not be enough glutathione to completely get rid of N-acetyl-p-benzoquinone imine, causing toxicity!

Propionic acid derivatives:

Ibuprofen, naproxen, fenoprofen, flubiprofen, ketoprophen and oxaprozin,

Oxaprozin: longest half-live, once or twice daily administration

Action: Anti-inflammatory, analgesic, antipyretic, and anti-platelet.

Usually we do not prescribe it as anti-platelet, since if the patient was taking heparin/warfarin (anti-coagulants), there will be a drug interaction which will prolong action of the drug and result in severe side effects.

Properties of the drug:

- ✓ Low toxicity
- ✓ Good action as anti-inflammatory in the chronic form of rheumatoid arthritis
- ✓ GIT toxicity less than aspirin
- ✓ Reversible inhibition of COX. (if you stop taking the drug, you do not have to wait for the renewal of platelets like in aspirin)

Naproxen is the safest drug.

Pharmacokinetics:

- ✓ Absorption: Well absorbed after oral administration.
- ✓ Distribution: These drugs are totally bound to blood/plasma proteins. Thus, you should take drug-drug interactions into consideration when you prescribe them, especially with Warfarin.
- ✓ Metabolism: hepatic metabolism.
- ✓ Excretion: in urine.
- ✓ Half-Life: oxaprozin has the longest half life. It is administered once daily.

Side Effects:

- ✓ GIT: dyspepsia, which leads to bleeding.
- ✓ CNS: Headache, dizziness, tinnitus.

Acetic Acid Derivatives:

Indomethacin, Sulindac, Tolmetin, etodolac.

Indomethacin is an old drug, and a powerful anti-inflammatory. However, it has three problems that prevent it from being the first choice anti-rheumatic drug.

- ✓ May lead to heart failure.
- ✓ CNS effects because it passes Blood-Brain Barrier
- ✓ May cause GIT bleeding.

Action:

- ✓ Very potent anti-inflammatory
- ✓ analgesic
- ✓ antipyretic

Therapeutic Use:

- ✓ Used only after less toxic agents have proven ineffective.
- ✓ Toxicity limits its use.
- ✓ Not used as antipyretic or for gout.

Oxicam Derivatives:

Piroxicam and meloxicam.

Therapeutic Uses:

- ✓ Rheumatoid arthritis.
- ✓ Ankylosing spondylitis.
- ✓ Osteoarthritis.

Pharmacokinetics:

- ✓ Half-Life: long. administered once daily.
- ✓ Renal elimination & metabolism [not clear in recording]
- ✓ Side Effects: GIT
- ✓ Inhibits both COX-1 and COX-2. (it is non-specific)

Fenamates:

Metenamic acid and Meclofenamic acid. They are anti-inflammatory drugs.

- ✓ Side Effects: diarrhea (can be severe), bowel inflammation, hemolytic anemia.
- ✓ It will only be given for RA patients if other drugs fail.

Celecoxib:

COX-2 inhibitor. However, it is relative specificity; it becomes a nonspecific COX inhibitor if doses are increased. This drug could lead to infarction of the heart.

Mechanism of action:

- ✓ It's more elective for COX-2 than COX-1.
- ✓ It's inhibition of COX-2 is time dependent and reversible.
- ✓ It has no effect on platelet aggregation.

Therapeutic Uses:

- ✓ Rheumatoid Arthritis
- ✓ osteoarthritis
- ✓ pain
- ✓ Patients with gastric ulcers. Because it doesn't inhibit COX-1 when given in small doses.

Pharmacokinetics:

- ✓ Well absorbed from GIT.
- ✓ Extensively metabolized in the liver by CYT-p450 system.
- ✓ Excreted in feces and urine. [not clear in recording]
- ✓ Half Life: about 11 hours.

Adverse Effects:

- ✓ Headache
- ✓ Dyspepsia
- ✓ Diarrhea
- ✓ Abdominal pain
- ✓ Allergy (sulfonamide allergy).

Avoid in:

- ✓ Kidney toxicity.
- ✓ Chronic renal insufficiency.

- ✓ Dehydration.
- ✓ Hepatic failure.
- ✓ Contraindicated in Cardiovascular diseases and when doing grafts of coronaries.

Drug Interactions:

- ✓ β-blockers
- ✓ antidepressants
- ✓ antipsychotics

GOUT

It's a metabolic disease caused by the overproduction of uric acid (from catabolism of proteins and nucleic acids → xanthines), low excretion of uric acid, or both (thus, it's recommended not to eat meat). It leads to the precipitation of sodium urate crystals in the tissues (especially joints, in the synovial membranes). It usually occurs in the joint of the big toe and causes inflammation and extreme pain. It leads to activation of leukocytes and invasion of lymphocytes, producing leukotrienes and cytokines which lead to swelling, redness, pain, and hotness. When precipitation occurs as urate stones in the kidney, it may lead to renal failure. If the urate stones reach the ureter, it's highly painful. And it may lead to hypertension by getting into the blood vessels as well.

Most therapeutic strategies of gout involve interfering with uric acid *synthesis* or increasing uric acid *excretion*.

Allopurinol: inhibits the synthesis of urate

- ✓ Not useful in acute cases (may make them worse).
- ✓ Inhibits synthesis of urate, especially in liver.

Mechanism of Action:

- ✓ Inhibition of xanthine oxidase enzyme >> less uric acid synthesis >> less urate crystal deposition in tissues >> reduced formation of urate renal stones.
- ✓ It's the drug of choice for treatment of chronic gout.

Kinetics:

- ✓ Administered orally.
- ✓ Well absorbed.
- ✓ Hal life: 2-3 hours
- ✓ Excretion: Renal. Through urine.

Colchicine:

- ✓ Used in acute gout attacks
- ✓ Prevention
- ✓ Treatment
- ✓ Acts on neutrophils
- ✓ The doctor thinks it's been discontinued.

Kinetics:

- ✓ Administered orally.
- ✓ Well absorbed
- ✓ Excreted mainly through GIT and partly by urine.

Unwanted Effects:

- ✓ Nausea
- ✓ Vomiting
- ✓ Abdominal pain
- ✓ Diarrhea
- ✓ Hemorrhage
- ✓ Kidney damage
- ✓ Rashes
- ✓ Peripheral neuropathy
- ✓ Blood dyscrasia

This was not mentioned by the doctor:
Blood dyscrasia is a nonspecific term for a defect in blood. The defect could be in one of the normal blood constituents.

Uricosuric Drugs: Increase elimination of uric acid through kidneys.

"The line of treatment is by uricosuric and anti-inflammatory drugs that inhibit prostaglandins and thus symptoms of inflammation. Effects on the *periphery* are anti-inflammatory (analgesics & antipyretics), effects on the *kidney* include increased excretion of uric acid through urine, and thus decreasing its concentration in the blood and tissues."

" We learn, not by reading sheets, not by going to school, not by listening to other people, we learn, by making our own path, even if we get lost several times. "

-A.K