PASSION ACADEMIC TEAM

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Sheet# 5

YU - MEDICINE

GASTROINTESTINAL SYSTEM

Lec. Title : Drug-Induced of Hepatotoxicity .

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Drug-induced Hepatotoxicity

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DRUG-INDUCED LIVER INJURY / DISEASE (DILI)

Liver injury may be produced by a large variety of chemical substances

The type and degree of injury produced is extremely varied, and may mimic the entire spectrum of hepatobiliary disorders.

The central role played by the liver in the clearance and biotransformation of chemical → susceptibility to drug-induced injury.

Drugs can initiate progressive chronic liver disease and are the single leading cause of acute liver failure.

Friedman, S.L., McQuaid K.R., 2003, Current Diagnosis and Treatment in Gastroenterology, USA: The McGraw-Hills, Comp.

Sheet #1

. The liver is the main place to metabolize drugs, so there are certain drugs the affects the liver and known to be HEPATOTOXIC

. Liver injury May be produced by a large variety of chemicals and this injury is classified Into→

1-)***Type***---A-Make the bile Flow slowly(cholestatic jaundice) Ex:Steroids+oral contraceptives

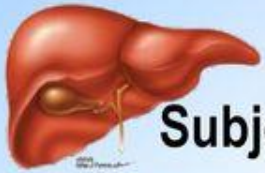
B-Acute liver necrosis Ex: Paracetamol

2-)***Degree***-A-Fulminant hepatic injury

B-Chronic injury withstanded by the Patient

. Most common causes for acute liver failure is the exposure to the drugs which makes liver more susceptible to chronic diseases followed by ACUTE liver damage because the patient takes drugs over a period of time so the damage is progressive and may enter acute phase

But the patient might take a toxic dose from the beginning so he enters acute phase directly .



HEPATOTOXIC DRUGS

Subjects drugs to chemical transformation (METABOLISM) ➔ to become inactive & easily excreted. Since most drugs are lipophilic ➔ they are changed into hydrophilic water soluble products ➔ suitable for elimination through the bile or urine

Such metabolic transformation usually occur in 2 PHASES:

Phase 1 reactions
Oxidation, Reduction, Hydrolysis, Hydration
Catalyzed by CYT P-450

Yields intermediates ➔
polar, transient, usually highly reactive ➔
far more toxic than parent substrates ➔
may result in liver injury

Drug Induced Liver Injury (DILI)

Phase 2 reactions
Conjugation with a moiety (acetate, a.a., glutathione, glucuronic a., sulfate)

Yields products of increased solubility
If of high molecular weight ➔ excreted in bile
If of low molecular weight ➔ to blood ➔ excreted in urine

Sheet #2

The purpose of metabolism of drugs is to transfer the active Hydrophobic to *Inactive Hydrophilic* .The metabolism has two phases-Phase 1 and Phase 2-Some drugs are only metabolized by phase 1,others go to phase 1 then phase 2,and some goes directly into phase 2,and lastly some drugs are metabolized by phase 2 then phase 1 such as Isonized

Phase 1 by CYT –P450 which involves chemical reactions such as:Oxidation,reduction,Hyrdation,hydrolysis→which leads to an intermediated drug that is polar and highly reactive than the drug itself which leads to liver injury

Phase 2 by adding a group to the drug by conjugation such as(Sulfate,acetate,glutathione,glucuronic)which give products that are hydrophilic+inactive polar compound
also if the product has LOW MW→urine excertion
If it has High MW→Bile excretion

Drug-induced Liver Disease (DILD)

- **Predictable**
  - **Dose related**
  - **Intrinsically hepatotoxic drugs**
  - **Acute (hours)**
  - **Injury pattern is usually necrosis**
  - **Clinically** → Fulminant (Acute Hepatitis)
  - **Example: Acetaminophine**

- **Unpredictable**
  - **Not dose related**
  - **Rare 0.01-1.0 %**
  - **Weeks to months after ingestion of drug**
  - **Idiosyncratic**
    - **Immune mediated idiosyncrasy (Hypersensitivity)**
      - **Rash**
      - **Fever**
      - **Arthragia**
      - **Eosinophilia**
      - **Example: Phenytoin, Sulfonamides, Valproate**
    - **Metabolic idiosyncrasy (Production of toxic metabolites)**
      - **Example: INH, Ketoconazole, and Diclofenac**

Sheet #3

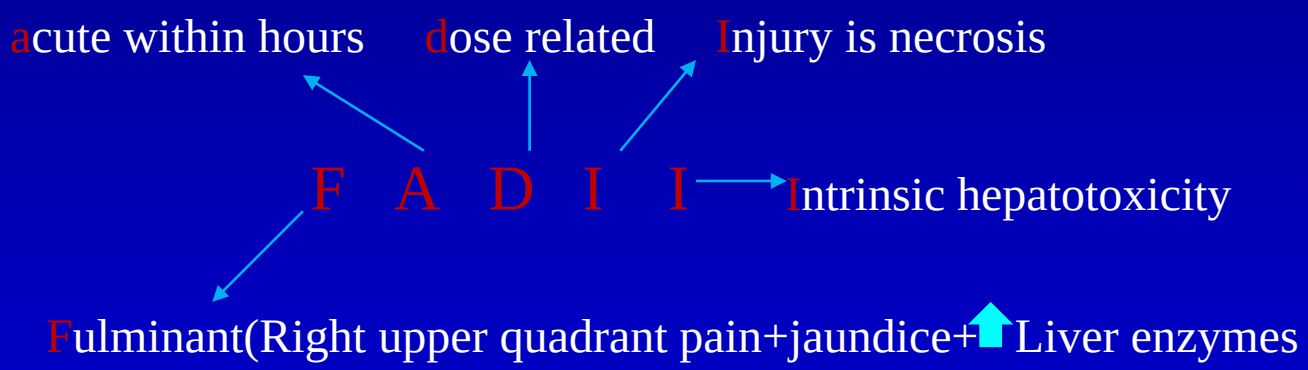
Unpredictable:The drug is given in a normal does but an unexpected reaction occurs it takes weeks to months and it could be caused by 1.) immune mediated Hypersensitivity reaction and what happens is that the body rejects the drug and causes the hypersensitivity reactions

Ex:Sulfonamide (ركز عليه),valproate,phenytoin

2.)Genetic polymorphism: What happens is that the liver puts toxic metabolite either by slow or rapid drug metabolism which is different from person to another Ex:isonized(مهم)

the unpredictable route has these features:1.Not dose related 2.Idiosyncratic 3.Rare 4.Weeks to months till the reaction occur

DILD



Predictable:The drug is known to cause hepatotoxicity at high dose فادي بنجمع الخواص باسم

Ex:Acetaminophin(paracetamol) ركز عليه كثير

Diagnosis of (DILD)

- **High index of suspicion**
- **Abnormalities in hepatic associated enzymes**
- **Hepatitis like symptoms**
- **Jaundice**

- **Drug history**
  - Dose
  - Duration of therapy
  - Time between initiating therapy and the development of hepatic injury (latency)

- **Exclusion of other causes of liver diseases**
  - Hepatitis B
  - Hepatitis C
  - Alcoholic liver diseases
  - Non alcoholic fatty liver diseases
  - Hemochromatosis

Sheet #4

1.)we must know the patient history for example if he is alcoholic or elder then he is at high risk

2.)Abnormality in hepatic enzyme→alkaline phosphatase (ALP) and Alanine transaminase(ALT)

3.)Hepatits like symptoms 4.)Jaundice

Drug history:1.)we ask the patient how much dose he has ingested

2.) الفترة الي اخذ فيها العلاج 3.)latency is the time between starting the therapy and developing hepatic injury Ex:Paracetamol→it needs 24 hours so the toxicity symptoms kick in

Diagnosis of (DILD)

- Most cases of acute DILD occurring within 1 week to 3 months of exposure

بصير عندنا حالتين لو وقفنا العلاج

- Positive response to discontinuing the agent (Dechallenge)
  - In acute hepatocelluler injury
    - 50% reduction in hepatic –associated enzymes after 2 weeks
    - Return to normal by 4 weeks
  - In cholestatic injury
    - May have prolonged recovery time

Risk Factors For Susceptibility to DILD

- Methotrexate
  - Alcohol
  - Obesity
  - D.M
  - Chronic hepatitis
- INH
  - HBV,HCV,HIV
  - Alcohol
  - Older age
  - Female
- Acetaminophen
  - Alcohol
  - Fasting
  - INH
- Valproate
  - Young age
  - Anticonvulsants
- Diclofenac
  - Female
  - Osteoarthritis

Sheet #5

Methotrexate-→Immunosuppressive+anticancer and an important drug in ulcerative colitis and chrons disease

INH→Is known to cause hepatocellular necrosis in persons who are rapid acyetylators(genetic polymorpyism)

Diclofenac→nonsteroidal drug

Anticonvulsant drugs→Ex:valproate+phenytoin+carbamazepine(commong in young)

Hepatotoxic Drugs

Patterns of drug-induced liver Injury			
Type of injury:	Hepatocellular	Cholestatic	Mixed
ALT	≥ Twofold rise	Normal	≥ Twofold rise
ALP	Normal	≥ Twofold rise	≥ Twofold rise
ALT: ALP ratio	High, ≥5	Low, ≤2	2-5
Examples	Acetaminophen Allopurinol Amiodarone HAART NSAID	Anabolic steroid Chlorpromazine Clopidogrel Erythromycin Hormonal contraception	Amitriptyline Enalapril Carbamazepine Sulfonamide Phenytoin

Sheet #6 (سلايد كثيير مهم)

Hepatocellular necrotic durgs 1.)Acetaminphin 2.)Nsaid 3.)HAART→highly active retro viral transcriptase(HIV medication) 4.)allopurinol 5.)amiodarone

Cholestatic drugs:1.)Anabolic steroid 2.)hormonal Contraceptives 3.)erythromycin 4.)chlorpromazine(anti psychotic)

Mixed:1.)phenytoin 2.)carbamazepine 3.)sulfonamide

الجدول كثير مهم يعني لو عندي Paracetamol toxicity بنتوقع انه يكون ALT>ALP

Drug-induced hepatotoxicity

Table 2

Drugs with Dose-Dependent Hepatotoxicity

Drugs	Hepatotoxicity
Acetaminophen	Hepatocellular necrosis due to single toxic dose or total dose over time
Amiodarone	Chronic steatosis due to total dose over time
Bromfenac	Toxicity after extended administration
Cyclosporine	Cholestasis with toxic blood levels
Methotrexate	Elevated aminotransferase and fibrosis after single or large total dose
Niacin	Vascular injury after large doses
Oral contraceptives	Hepatic tumor after prolonged administration
Tetracycline	Steatosis after large total dose and renal dysfunction

Table 4

Drugs Known to Cause Hepatocellular Necrosis

Drug Class	Drugs
Antimicrobials	Sulfonamides, dapsone, ketoconazole, isoniazid, rifampin, pyrazinamide
Anticonvulsants	Phenytoin, valproic acid, carbamazepine, felbamate
NSAIDs and analgesics	Acetaminophen, piroxicam, diclofenac, sulindac, etodolac, bromfenac
Miscellaneous	Labetalol, flutamide, disulfiram, propylthiouracil, pemoline, nefazodone

Table 5

Drugs Known to Cause Cholestasis

Drug Class	Drugs
Antimicrobials	Ampicillin, amoxicillin/clavulanate, clindamycin, erythromycin, tetracycline, trimethoprim-sulfamethoxazole
Psychotropics	Chlorpromazine, amitriptyline, barbiturates, carbamazepine, haloperidol, imipramine
Miscellaneous	Azathioprine, ibuprofen, cimetidine, prochlorperazine, ticlopidine, estradiol

Jiwon Kim. An Overview of Drug-Induced Liver Disease US Pharm. 2005;11:HS-10-HS-21.
http://www.uspharmacist.com/index.asp?show=article&page=8_1634.htm

Sheet #7

What is included in TABLE 2 are..

1.)Acetaminophen→it induced hepatocellular necrosis either by→A)one single high dose

B)Total dose over time((تراكمية)على مدار اليوم كانت الجرعة كبيرة)

2.)Methotrexate→Increases liver enzymes and causes FIBROSIS in the liver after single toxic dose or total dose over time

3.)Niacin causes blood vessels injury in the liver when administered at large doses

4.)oral contraceptives→hepatic tumor after long administration and also causes cholestatis

5.)tetracyclin→steatosis+renal dysfunction

Sheet #8

What is included in TABLE 4 are..

Drug induced hepatocellular necrosis

1.)antimicrobials (حفظ الادوية) #dont forget that sulfonamide is MIXED

2.)anti convulsants→also mixed (necrosis وهمو اكثر اشي بعملو)

3.)NSAID(Diclofinac)+analgesics(don't forget that acetaminophen is an analgesic NOT Nsaid)

What is included in TABLE 5 are..

1.)antimicrobial لانها mixed,the most important antimicrobial that cause statis is Erythromycin

2.)psychotropic→only cholestatis+الامثلة مطلوبة

Paracetamol-induced hepatotoxicity

Therapeutic and Toxic Dose

- Therapeutic dose: 10-15 mg/kg
- Toxic dose:
  - More than 7.5 gm(around 15 tablets)- minimal toxicity
  - If >15 gm (30 tablets)- severe toxicity
  - In adult- toxic dose is 150 mg/kg
  - In children, toxic dose is 200 mg/kg
  - In presence of chronic disease or malnutrition, even 2gm of paracetamol can be a toxic dose

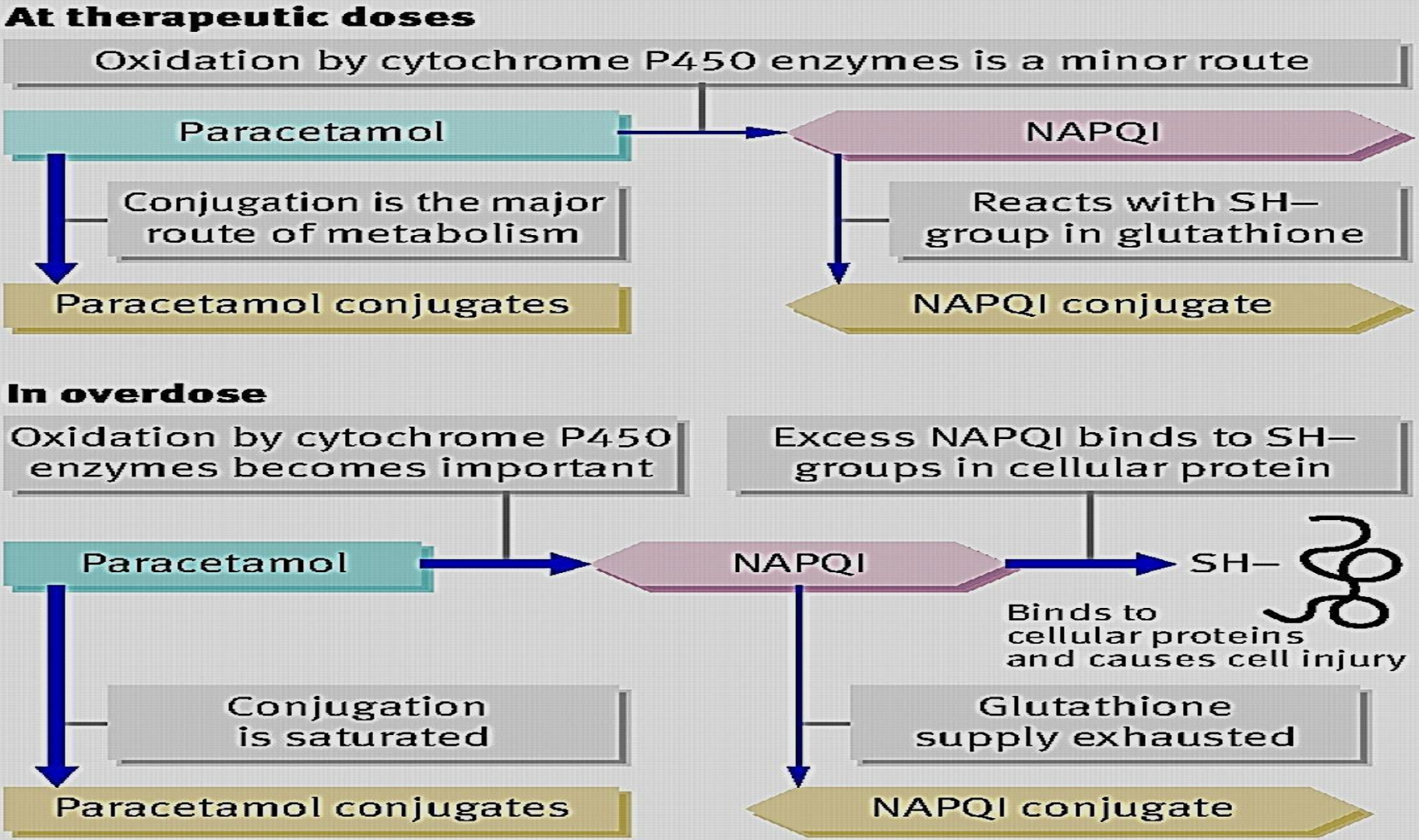
Sheet #9

15 tablets(7.5g)→minimal toxicity ما حكا اشي برا السلايد بس اذا باليوم الواحد اخذ المريض

30 tablets(15g)→Severe toxicity

#لو المريض عندو الكبد تعبان او عنده امراض اخرى الTox dose changes to 2gm

Paracetamol-induced hepatotoxicity



Sheet #10

The major route of metabolism of paracetamol is conjugaton and thus the product after metabolization is soluble →in case of normal therapeutic dose

In case of high dose what happens is that not all of the drug is conjugated and some parts of it will be oxidized in phase 1 and gives rise to An intermediate which is NAPQI and this intermediate starts searching for **Glutathion** in liver because it has SH group,so if NAPQI doesn't find glutathione then it becomes toxic and causes LIVER DAMAGE

Paracetamol-induced hepatotoxicity

Stages of acetaminophen toxicity			
Stage	*Time*	*Liver effects*	*Signs & Symptoms*
1	0-24 hrs	Preclinical	• General malaise • Nausea and vomiting • Diffuse abdominal pain • Possibly asymptomatic • Minimal signs and symptoms • Normal liver function tests, possibly
2	24-72 hrs	Hepatotoxicity	• RUQ pain, possibly • Clinically asymptomatic, possibly • AST and ALT begin to rise, and possibly bilirubin • Coagulopathy studies (PT, PTT, INR) may increase, if severe injury

3	72-96 hrs	Hepatic failure with encephalopathy	• Liver function tests peak
			• Clinical signs and symptoms of liver failure are evident, including:
			  • Jaundice
			  • Vomiting
			  • GI upset
			  • Coagulopathy
			  • Encephalopathy
			  • Metabolic acidosis
			  • Pancreatitis, possibly
			  • Acute renal failure, possibly

4	> 96 hrs	Survival or death	• Full resolution of hepatotoxicity, or • Multi-organ failure and death

Source: Farcy DA, Chiu WC, Flaxman A, Marshall JP: *Critical Care Emergency Medicine:* www.accessemergencymedicine.com

Sheet #11

Stage 1→0-24h hours,Normal liver enzymes(مهم),Often asymptomatic

Stage 2→24-72h liver enzymes starts to increase AST+ALT also Partial thromboblastin time(PPT) is increased and CPT

Stage 3→72-96h liver function test shows a peak of liver enzymes and CNS Symptoms occur and the most important one is Encephalopathy→it happens because the liver can't change ammonia to urea so ammonia accumulates and interferes with ATP production in the brain

Also it may affects kidney and causes Acute renal failure

Stage 4→Either the patient Survives if he was administrated fast and did Gastric lavage and took antidiotes ☺ OR the DIE in case of multi organ failure ☹

Paracetamol-induced hepatotoxicity

Treatment

Initial treatment :

- Basic life support (ABCs)
- Decontamination with activated charcoal (within 1-2 hr of ingestion)
- The antidote for acetaminophen poisoning is *N*- acetylcysteine (NAC) (which works primarily via replenishing hepatic glutathione stores)

http://www.drclarkstore.eu/images/P/45171-Activated-Charcoal.jpg

www.iherb.com

Sheet #12

1.)We give the patient basic life support such as checking The airways and respiration+Heart checking

2.)Activated charcoal→only effective after 1-2 hours of ingestion

3.)We give N-acetylcysteine(NAC) as an antidiote for paracetamol because it react with it and form an inactive product(its main job is to replensh the glutathione stores)


Thank
you!!