The Leeds Teaching Hospitals NHS
NHS Trust

Understanding the impact of liver dysfunction on drug use and when you need to worry

Penny North-Lewis
Paediatric Liver Pharmacist
Leeds Children's Hospital
November 2023

Can you use paracetamol in a liver patient?

MI problems

- Generally relate to drug choice and dose in a liver patient - 2/3rd
- Another 10% are for ADR/hepatotoxicity information
- Rest:
  - requests for protocol information
  - general background

Why the problem?

- Poor understanding of liver dysfunction and no easy equation

- Lack of information in regular sources e.g BNF, SPC

BNF: Reduce dose. Use with caution. Avoid. No information.
SPC: No information therefore avoid

- Lack of research, small numbers of patients with specific conditions

UDP-Glucuronosyltransferase activity

	Child-Pugh A[2]	Child-Pugh B[2]	Child-Pugh C[2]	NAFLD Animal[1]	NAFLD Human[1]
UGT1a	NS	⇩	⇩⇩ or NS	⇩ or ⇧	NS
UGT2b	NS	⇩	⇩⇩ or NS	⇩ or ⇧	NS

NS = not significant

1. Yan Zhu, Li Chen, Yuqi He *et al*. (2023) The alteration of drug metabolism enzymes and pharmacokinetic parameters in nonalcoholic fatty liver disease: current animal models and clinical practice. Drug Metabolism Reviews, 55:3, 163-180

2. Duthaler, U., Bachmann, F., Ozbey, A.C. *et al.* (2023) The Activity of Members of the UDP-Glucuronosyltransferase Subfamilies UGT1A and UGT2B is Impaired in Patients with Liver Cirrhosis. *Clin Pharmacokinet* **62**, 1141–1155

First principles

- Identify extent and type of liver dysfunction
- Consider how this will affect drug handling
- Consider how the drug may affect the patient – side effects, pharmacodynamic effects
- Remembering the whole patient

Aim

Understand the principles of drug use in patients with liver dysfunction

Learning outcome

Be able to advise on drug choice and dose for a liver patient by taking into account

- the degree of liver dysfunction
- the pharmacokinetics of the drug
- the side effect profile.

Can you use paracetamol in a liver patient?

- No – why not?
- Yes – why?
- Don’t know?
- An impossible to answer question??

- What do you need to know to be able to answer this question?

Disease *vs* dysfunction?

- Examples??

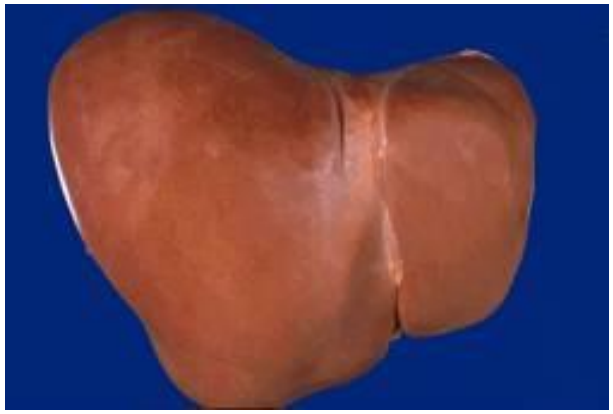
Causes of liver disease

- Metabolic & inherited – CF, Alagille, tyrosinaemia, Wilson's, Gilberts
- Autoimmune – AIH, PSC
- Structural – biliary atresia
- Infection – hepatitis B, C
- Non-alcoholic fatty liver disease
- Alcoholic liver disease
- Cancer (hepatoblastoma/HCC)

Causes of liver dysfunction

- Ischaemia
- Infection – H1N1, CMV, EBV, malaria…
- Multi-organ failure
- Drugs, parenteral nutrition
- Trauma
- Oncological – metastases
- Gallstones, pancreatitis

Terminology - Hepatocellular



- **Hepatitis**
  - Inflammation of hepatocytes
- **Fibrosis**
  - An increase in connective tissue in the liver – reversible

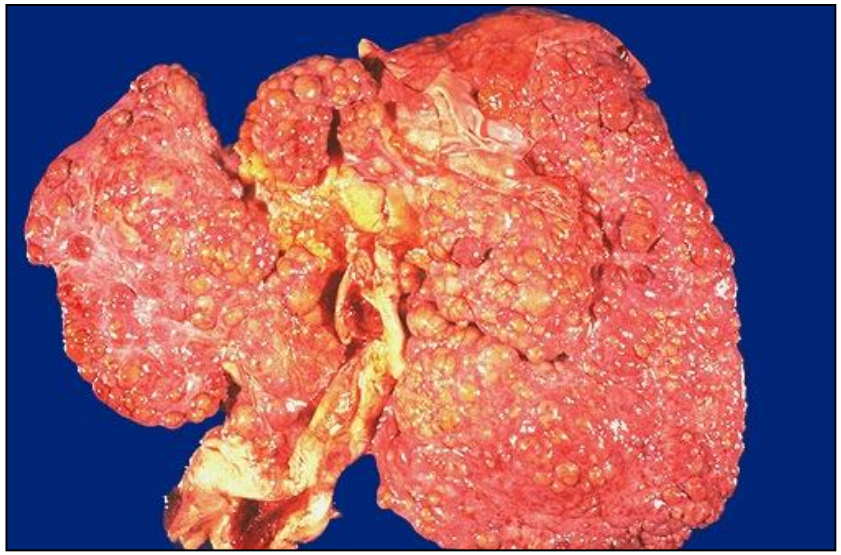
Terminology - Hepatocellular

- **Cirrhosis**

Widespread disorganised nodules in the liver combined with fibrosis

  - **Compensated cirrhosis**

    When a cirrhotic liver continues to function



Terminology - Hepatocellular

- **Cirrhosis**

Widespread disorganised nodules in the liver combined with fibrosis

  - **Compensated cirrhosis**

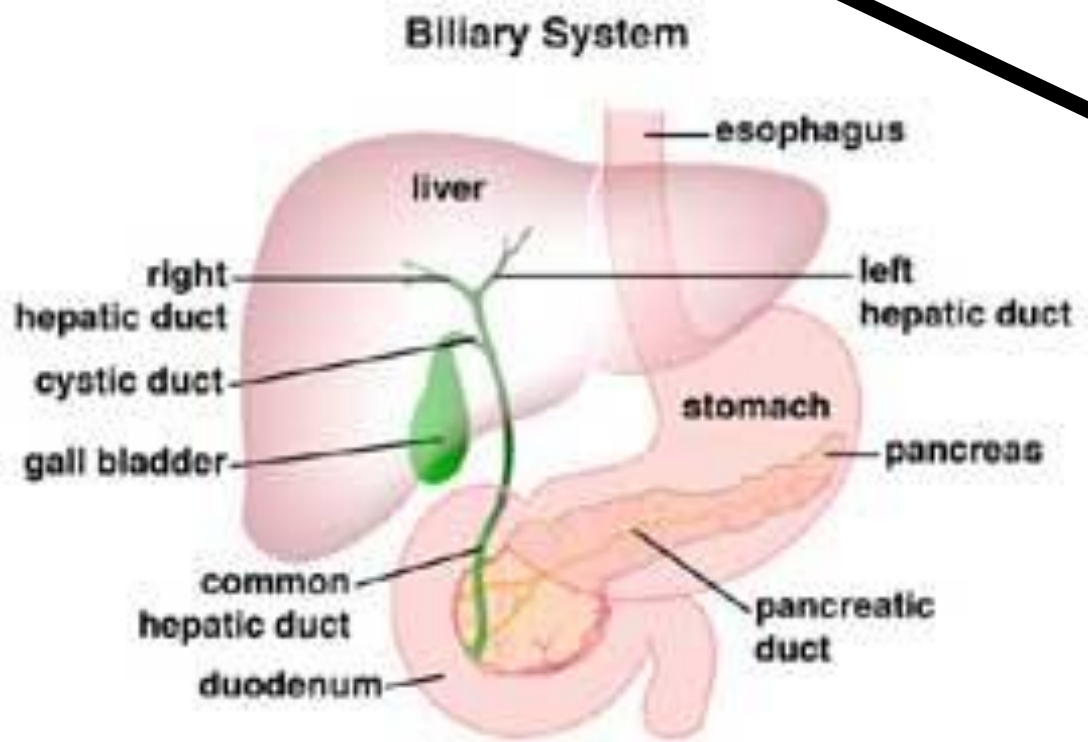
  When a cirrhotic liver continues to function

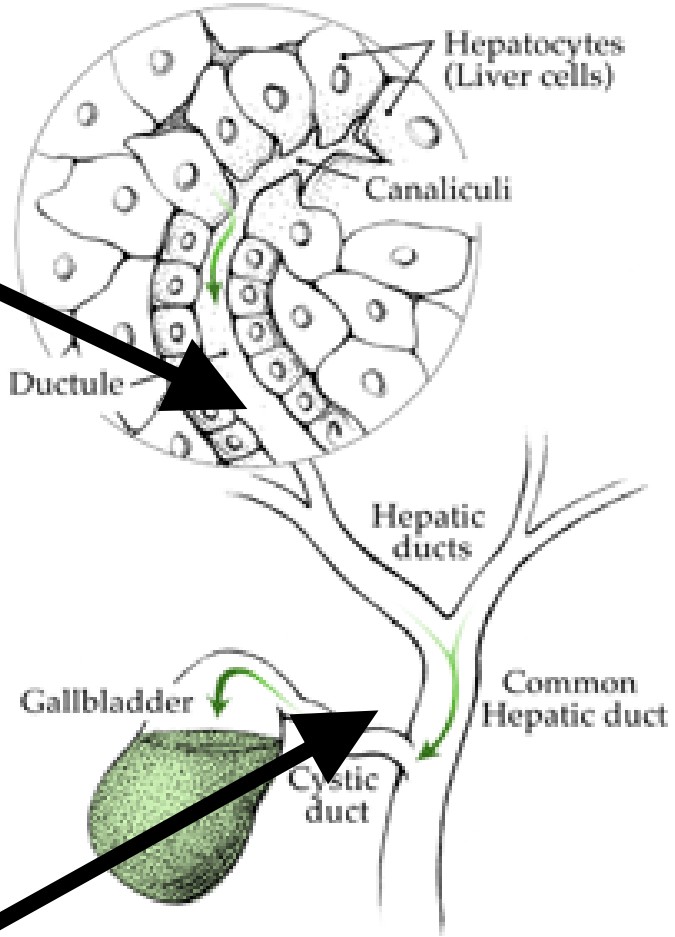
  - **Decompensated cirrhosis**

  When a cirrhotic liver can no longer function adequately – signs eg coagulopathy occur

Cholestasis

Intrahepatic





Extrahepatic

LFTs??

- Which are they?
- What do they do?
- What do they mean?

Transaminases (0-35iu/L) (ALT & AST)

- Enzyme released from hepatocytes when damaged
- Markers of hepatocellular injury
  - High elevations in acute injury (in several thousands)
  - Can be **normal** in severe chronic liver disease (cirrhosis)

Bilirubin (3-20 micromol/l)

Unconjugated

- Increased production (haemolysis)
- Decreased conjugation (Gilberts, neonate, cirrhosis)

Conjugated

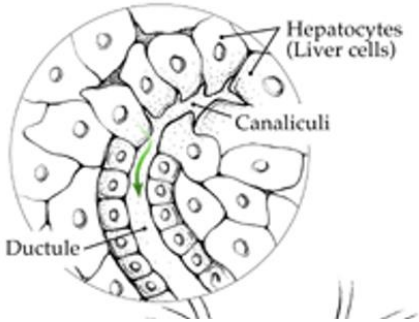
- Intrahepatic cholestasis
- Extrahepatic cholestasis (gall stones, BA)

Haem of erythrocytes
↓
bilirubin
↓
plasma
↓
albumin (unconjugated)
↓
hepatocyte (conjugated & water soluble)
↓
bile
↓
faeces

Alkaline Phosphatase

(normal range varies for age and hospital)

- Biliary enzyme – produced in the hepatocyte but raised with bile duct damage
  - Increased in cholestasis



- Not specific to the liver
  - also found in bone (e.g. raised in growing children, Paget's disease/bone metastases/hepatic osteodystrophy – vitamin D deficiency)
  - small quantities in the intestine and placenta

Gamma glutamyl transferase (GGT) (0-30iu/l)

- Enzyme in biliary epithelial cells and hepatocytes
  - Increased in cholestasis
- Increased by enzyme inducing drugs e.g. rifampicin and alcohol
- Useful to determine if isolated raised alkaline phosphatase is liver related

Prothrombin Time (~13 secs) or INR (0.9-1.2)

- Decreased synthesis of clotting factors

OR

- Vitamin K malabsorption

- Useful prognostic indicator of impending liver failure e.g. acute liver failure or decompensated chronic liver disease

Albumin (35 – 50g/L)

- Synthesised in liver
- Half-life approx 20 days
- Good indicator of chronic liver disease
- Low specificity
  - Decreased intake e.g. malnutrition
  - Increased loss e.g. enteropathy

Other potentially useful tests

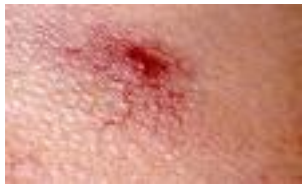
- Ultrasound – liver texture, dopplers for blood flow in hepatic artery, portal vein
- Liver biopsy – fibrosis, cirrhosis, intrahepatic cholestasis, active or burnt out
- OGD – varices
- Blood glucose, creatinine, ammonia
- HIDA – bile flow (cholestasis)

Signs and symptoms?

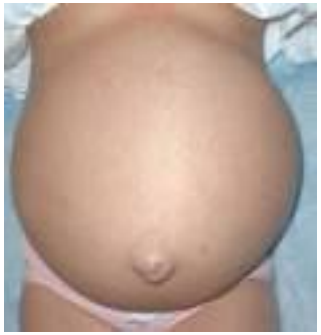
Signs of liver dysfunction

- Jaundice
- Pale stools/dark urine
- Failure to thrive
- Palmar erythema
- White nails
- Spider naevi
- Ascites
- Steatorrhoea
- Hepatomegaly
- Splenomegaly
- Oesophageal and gastric varices
- Encephalopathy

Jaundice



“Spiders”



Ascites

Symptoms of liver dysfunction

- Pruritus
- Lethargy
- Abdominal pain
- Bruising and bleeding
- Anorexia

- ALT 34
- INR 1.3

= normal

- With spider naevi = cirrhosis (compensated)
- With spider naevi and encephalopathy = decompensated cirrhosis

Categorising patient into one of the following types helps plan response:

- Hepatitis
- Cholestasis
- Cirrhosis – compensated
- Cirrhosis – decompensated
- Acute liver failure

What kind of liver disease is this?

- ALT 123
- Alk Phos 295
- Bilirubin 17
- Albumin 38
- INR 1.1
- Hepatomegaly
- Recent history of viral infection

Hepatitis – acute

What about this one?

- ALT 123
- Alk Phos 295
- Bilirubin 17
- Albumin 38
- INR 1.1
- Hepatomegaly
- Intermittent abdo pain over last few months, lethargic

- Liver biopsy – steatosis
  = Non-alcoholic fatty liver disease

Hepatitis – chronic

And this?

- Bilirubin 120
- Alk Phos 768
- GGT 194
- ALT 38
- Albumin 47
- INR 1.2

Cholestatic

And now?

- Bilirubin 195 ^
- Alk Phos 973 ^
- GGT 203 ^
- ALT 38
- Albumin 47
- INR 2.3 ^
- Pruritus, pale stools, dark urine
- Failure to thrive, fat soluble vitamin deficiencies

Severe cholestasis

- ALT 34
- Alk Phos 450
- GGT 103
- Bilirubin 53
- Albumin 25
- INR 1.5

Compensated cirrhosis

- Varices, mild ascites – no diuretics
- USS – small nodular liver, low flow in portal vein

- ALT 34
- Alk Phos 850 ^
- GGT 103
- Bilirubin 300 ^
- Albumin 21
- INR 2.3 ^

Decompensated Cirrhosis

- Varices – occ bleeding, refractory ascites
- Intermittent encephalopathy

Next stage - drug considerations

- Pharmacokinetics
- Pharmacodynamics
- Adverse drug reactions

Absorption

- **Ascites** may impair absorption e.g. diuretics
  - Bigger doses or IV

- **Cholestasis** may impair absorption of fat soluble drugs e.g. fat soluble vitamins
  - Bigger doses

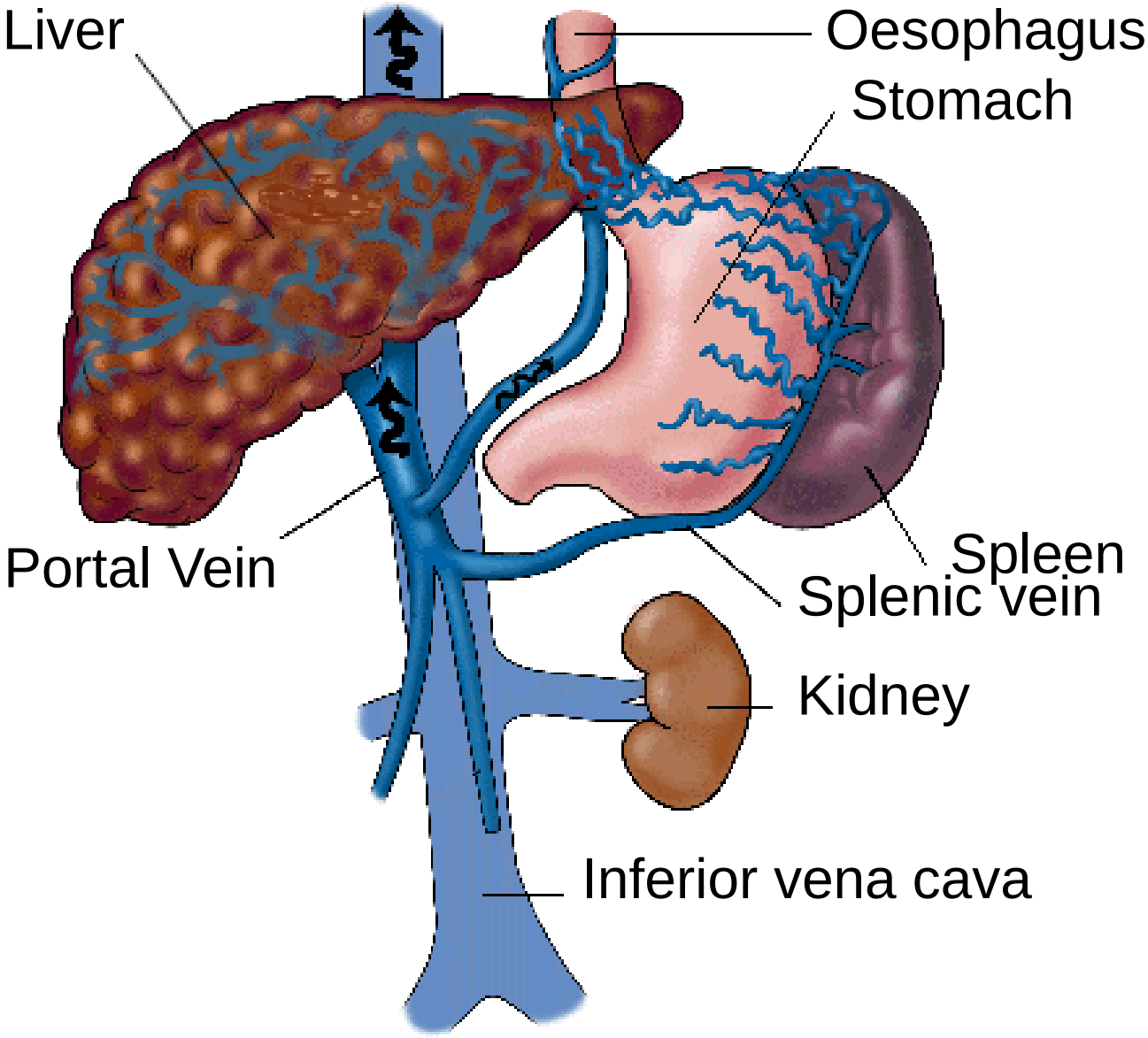
Distribution

- **Ascites** will increase volume of distribution for water soluble drugs
  - Bigger doses *per kg*
- **Low albumin** will alter amount of free drug if highly protein bound
  - Reduced doses

Metabolism

- **Decompensated cirrhosis or acute liver failure** - reduced number of functioning hepatocytes
  - Reduce dose or increase interval
- **Portal hypertension** - reduced first pass metabolism if highly extracted drug e.g. propranolol, lidocaine
  - Reduce dose

- Portal hypertension



Elimination

- **Cholestasis –** biliary cleared drugs may accumulate
  - Caution if active/toxic metabolites are produced, possibly not important if inactive
  - Compensatory pathways e.g. renal if reduced biliary clearance?

Pharmacodynamcis

- Increased receptor sensitivity
  - More permeable BBB, increase in circulating neurotoxins e.g. ammonia
    - Increased respiratory depression with opioids
    - Increased sedation with benzodiazepines

Side Effect Profile

Drugs with the following side effects may need to be avoided/used with caution:

- Pruritus
- Coagulation defects
- GI ulceration
- Constipation
- Effects on electrolytes and fluid balance
- Sedation
- Renal toxicity

Hepatotoxicity

Existing liver dysfunction does not increase risk of hepatotoxic reaction but makes it more difficult to manage (exceptions incl. valproate, MTX)

It may also make the hepatotoxic reaction more serious – higher mortality rates reported.

Hepatotoxicity

Has this drug caused hepatoxicity?

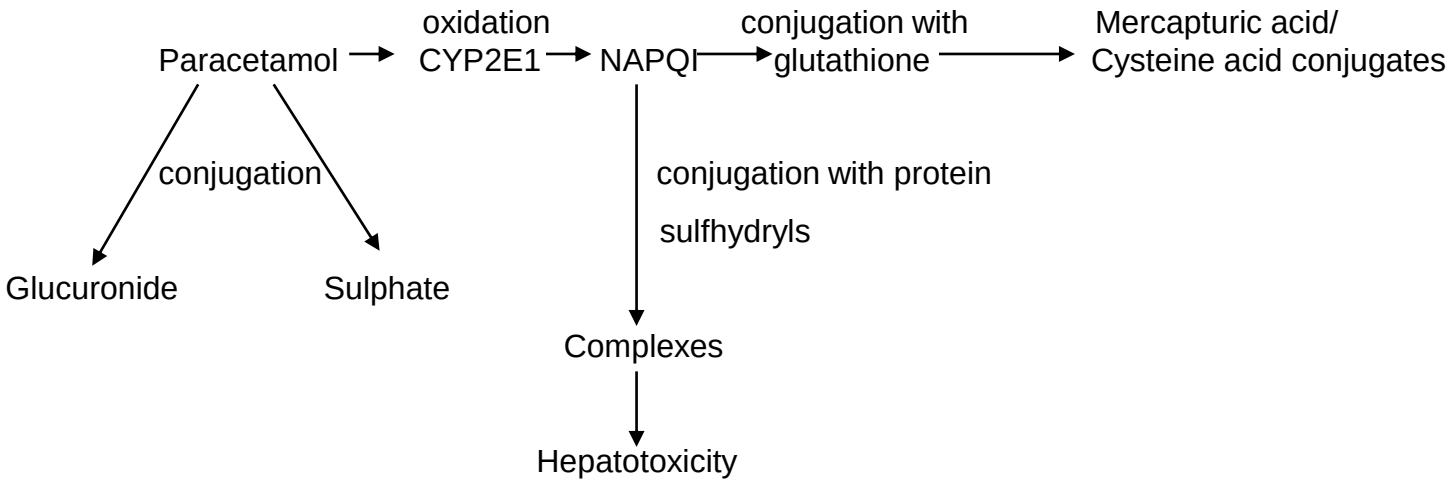
- livertox database - https://livertox.nih.gov/

Paracetamol

Hepatic metabolism (multiple pathways)

- Need glutathione – stores may be reduced in the severely malnourished

Hepatotoxic in overdose



Paracetamol

- Hepatitis - OK
- Cholestasis - OK
- Compensated cirrhosis - OK
- Decompensated cirrhosis
  - OK but reduce dose to tds (be aware of weight of patient)
- Acute liver failure
  - OK unless ALF is secondary to paracetamol overdose!!

Ibuprofen

- Lipid soluble
- 99% protein binding
- Extensive hepatic metabolism
- Side effects
  - GI ulceration
  - Inhibition of platelet aggregation
  - Renal impairment
  - Fluid retention and electrolyte abnormalities
  - Hepatotoxicity

Ibuprofen

- Hepatitis
  - OK unless INR raised

- Cholestasis
  - Possible impaired oral absorption (lipid soluble drug)
  - May displace bilirubin from protein binding sites or v.v.
  - Caution if pt has raised INR due to vit K malabsorption
  - Prefer avoid but could use with careful consideration

Ibuprofen

- Cirrhosis
  - Risk of bleeding, renal toxicity, sodium and water retention
  - AVOID

- Decompensated cirrhosis
  - Poor metabolism, accumulation
  - Bleeding risk, renal toxicity, fluid and electrolyte disturbance

- Acute liver failure

Morphine

- Low protein binding
- Extensive hepatic metabolism, first pass >50%
- Biliary excretion and enterohepatic recirculation
- Side effects?
  - Sedation, respiratory depression
  - Constipation
  - Pruritus

Morphine

- Hepatitis
  - Fine to use

- Cholestasis
  - Possible impaired excretion
  - Pruritus, bile duct spasm
  - Yes – normal dose but monitor and use prn

Morphine

- Compensated cirrhosis
  - Impaired metabolism possible accumulation
  - Varices may affect first pass
  - Sedation, resp depression – encephalopathy
  - No/Maybe – half dose but monitor and use prn with wider intervals
- Decompensated cirrhosis
  - Impaired metabolism/accumulation
  - Sedation, respiratory depression
  - No unless can be closely monitored – quarter to half dose, 8-12 hourly. If tolerated may increase dose but keep interval the same.

Morphine

- Acute liver failure
  - Impaired metabolism/accumulation
  - Sedation, respiratory depression highly likely
  - High risk of precipitating encephalopathy
  - ONLY use in ventilated patient. Ensure lowest rate is used once patient adequately loaded. May be difficult to extubate – prolonged effect.
    - Naloxone may help but caution when it is stopped as morphine distributes into fat and may take some time to fully clear (days)

Drugs in liver dysfunction – aide memoire

Patient Information

Name/DoB/unit number

Diagnosis (type/cause)(if known) _____

Relevant biochemical tests:

Test	Result - recent changes ↑ ↓ ↔	Normal Range
ALT/AST		
Bilirubin		
Split Bilirubin*		
Alk Phos		
GGT		
Albumin		
INR/PT		
Creatinine / creatinine clearance / GFR		

Caution: check for non-liver causes of abnormal results e.g warfarin, bone disease.
* May be useful in determining reason for hyperbilirubinaemia – not a routine test

Signs of liver disease and useful test results likely to have an impact on drug handling

Sign	Present?	Tests	Result
Gynaecomastia		Biopsy	
Ascites		ERCP/HIDA	
Varices		Ultrasound scan - dopplers	
Failure to thrive/ wt loss		Endoscopy	
Pale stools		Encephalopathy score/grade	
Encephalopathy		MELD/PELD/Childs Pugh	

Using all the information available, including the signs and test results, tick which apply with severity or grade if known

Effect on kinetics/dynamics		Risk factors for side effects	
Ascites (A/D)		Varices	
Cholestasis (A/E)		Coagulopathy or low platelets	
Low albumin (D)		Encephalopathy	
Portal hypertension (M)		Pruritus	
Acute liver failure (M)		Alcoholism	
Cirrhosis - compensated (M)		Ascites	
Cirrhosis - decompensated (M)		Renal impairment/hepatorenal	
Encephalopathy (P)		Cirrhosis	

Key A: Absorption D: Distribution M: Metabolism E: Elimination P: Pharmacodynamics

Drugs and the Liver, Ed. Penny North-Lewis, Pharmaceutical Press, 2008

Drug Considerations

Pharmacokinetics

		Considerations
Absorption		Lipid solubilty (Absorption affected by ascites)
Distribution		Water/fat Protein binding % Displaced by bilirubin or displaces bilirubin
Metabolism		First pass effect Hepatocyte dependent Prodrug CYPs Active metabolites Genetics
Elimination		Biliary excretion Alternative mechanisms Enterohepatic recirculation (Renal impairment)

Side effects
Consider – GI ulceration, sedation, coagulopathy, platelet effects, effects on fluid balance, effect on electrolytes, biliary sludging, renal impairment, constipation

Hepatotoxicity - known hepatotoxin/type

Concomitant drug interactions and other patient considerations e.g. age, renal function, contra-indications

Published information in specific liver diseases/clinical studies
BNF/SPC

Summary/Answer

Drugs and the Liver, Ed. Penny North-Lewis, Pharmaceutical Press, 2008

Key messages – when to worry

- Cirrhosis, esp decompensated
  - Metabolism, risk of encephalopathy, coagulopathy, nephrotoxicity
- Varices
  - First pass, bleeding risk
- Ascites, low albumin
  - Distribution

Summary

- Work out what is wrong with your patient's liver and how bad it is
- See if the pharmacokinetics of the drug you want to use could be affected
- Check the drug doesn't have side effects which could harm the patient

Sources of further information

- Medicines Q&As on SPS/NELM
- Drug PK data – Micromedex, Lexicomp, SPC, Martindale, Dollery
- Drugs and the Liver!

- Caution with interpreting references

- Safe use of medication in patients with cirrhosis: pharmacokinetic and pharmacodynamic considerations. Weersink RA, Burger DM, Hayward KL *et al*. Expert opinion on drug metabolism & toxicology 2020, Vol. 16, No. 1, 45–57

https://www.drugsinlivercirrhosis.org/healthcare-professionals/drugs/systemic-antihistamines/

Drugs in liver cirrhosis | Healthcare professionals

HOME DRUGS FAQ CONTACT

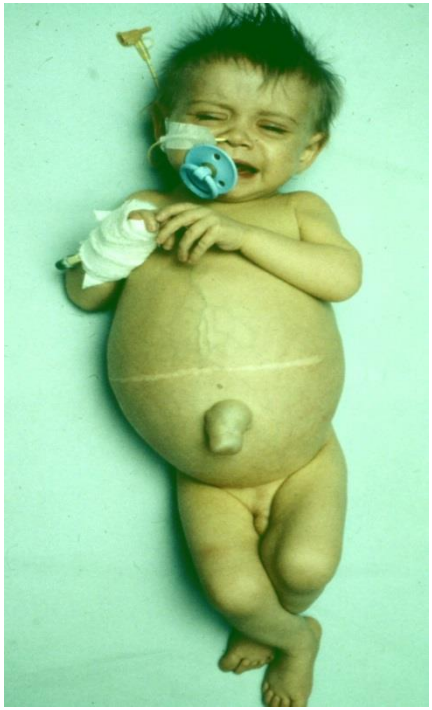
Search for medicines

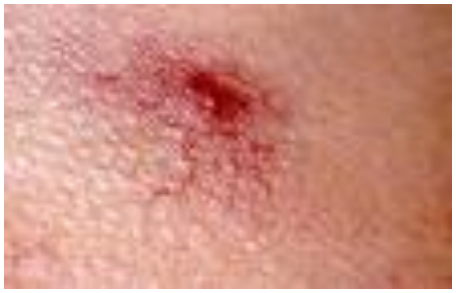
Systemic antihistamines

		Child-Pugh A	Child-Pugh B+C
Cetirizine	**Safety**	no additional risks known	no additional risks known
	Dose	use half of the normal dose	use half of the normal dose
Levocetirizine	**Safety**	no additional risks known	no additional risks known
	Dose	use half of the normal dose	use half of the normal dose
Desloratadine	**Safety**	no additional risks known	no additional risks known
	Dose	use half of the normal dose	use half of the normal dose
Loratadine	**Safety**	no additional risks known	no additional risks known
	Dose	use half of the normal dose	use half of the normal dose
Ebastine	**Safety**	no additional risks known	no additional risks known
	Dose	no dose adjustment needed	no dose adjustment needed
Fexofenadine	**Safety**	no additional risks known	no additional risks known
	Dose	no dose adjustment needed	no dose adjustment needed
Hydroxyzine	**Safety**	no additional risks known	unknown
	Dose	no dose adjustment needed	no dosing advice possible
Mizolastine	**Safety**	no additional risks known	unknown

Sedation – risk encephalopathy

Any questions?





Child-Pugh score – cirrhosis only

Score	1	2	3
SBr	<34	34-51	>51
Albumin	>35	30-35	<30
INR	<1.7	1.7-2.3	>2.3
Ascites	None	Easily controlled	Poorly controlled
Encephalopathy	None	Minimal	Advanced

A = 5-6 *(mild)*, B = 7-9 *(moderate)*, C ≥ 10 *(severe)*

Hepatitis – typical picture

Signs/LFTs

- Raised ALT 100-1000
- Possibly raised INR if severe
- Hepatomegaly

Symptoms

- Abdo pain - possibly

May develop fibrosis

Fibrosis – typical picture

Signs/LFTs

- Raised ALT 100-500
- Hepatomegaly or not (previous inflammation may have shrunk)
- Possibly splenomegaly
- Possibly mild ascites

Symptoms

- Lethargy

May develop cirrhosis

Cirrhosis - compensated

Signs/LFTs

- Normal or mildly elevated ALT 20-200
- Possibly cholestasis (raised bilirubin, Alk Phos, GGT)
- Raised INR 1.2-1.8
- Splenomegaly
- Ascites – mild to moderate but managed with diuretics
- Varices

Symptoms

- Lethargy
- Anorexia
- Bruising/bleeding

May decompensate

Cirrhosis - decompensated

Signs/LFTs

- Normal ALT
- Probably some cholestasis (raised bilirubin (unconjugated), Alk Phos, GGT)
- Raised INR 1.5-3
- Splenomegaly
- Ascites – refractory to diuretics
- Varices
- Encephalopathy
- Low blood glucose

Symptoms

- Lethargy
- Anorexia
- Bruising/bleeding
- Confusion

End stage

Cholestatic liver disease

Signs/LFTs

- Typically high bilirubin*, GGT and Alk Phos
- Failure to thrive
- Fat soluble vitamin deficiencies
- Steatorrhoea

Symptoms

- Pruritus
- Jaundice
- Pale stools, dark urine
- Smelly, oily stool
- Hungry

*May have normal bilirubin but high bile acids as just bile acids not excreted

May develop into biliary cirrhosis

Acute liver failure

Signs/LFTs

- Raised ALT: 1000-10,000 +
- Raised INR: 4-10 +
- Hepatomegaly
- Encephalopathy

Symptoms

- Abdo pain
- Lethargy

Query strategy part 1

- What picture/type of liver disease or dysfunction does the patient have?
  - Hepatocellular/cholestatic
  - Disease/dysfunction
- How bad is it (use LFTs, signs, symptoms, other tests to guide)?

Query strategy part 2

- Categorise patient
  - Hepatitis
  - Cholestasis
  - Cirrhosis
    - Compensated
    - Decompensated
  - Acute liver failure

Query strategy 3

- What drug characteristics does that mean need considering (ADME, ADRs)?

- Is the drug safe to use? What are the ADR risks in this patient?
- Does the dose need adjusting? Any PK considerations?
- What monitoring is required?