Medicines issues in liver disease

Penny North-Lewis
Paediatric Liver Pharmacist
Leeds General Infirmary
September 2011
Aim

- To illustrate some of the enquiries encountered regarding the use of medicines in patients with liver dysfunction
- To define a strategy for finding solutions to these queries
Plan for session

- Types of liver related MI enquiries
- Why it is so hard to answer them
- Basic hepatology
- Interpreting laboratory tests
- Pharmacokinetics and dynamics
- Pulling together an answer
Types of liver enquiry

- 152 enquiries from Apr 10 to Mar 11
  - 109 choice/dose of drug in a liver pt
  - 20 requests for protocol information
  - 9 for ADR/hepatotoxicity information
  - Others incl. compatibility, general background
<table>
<thead>
<tr>
<th>Types of liver enquiry – choice/dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobials</td>
</tr>
<tr>
<td>Analgesia</td>
</tr>
<tr>
<td>Psychotropics</td>
</tr>
<tr>
<td>Antiepileptics</td>
</tr>
<tr>
<td>Antidepressants</td>
</tr>
<tr>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Hormones</td>
</tr>
<tr>
<td>Others incl. antihistamines, antiemetics</td>
</tr>
</tbody>
</table>
Why the problem?

- Lack of information in regular sources e.g BNF, SPC (misinformation/lack of data)
- Lack of research, small numbers of patients
- No easy equation to use
- Poor understanding of liver dysfunction
Where to start

- Taking in an enquiry
  - Liver Enquiry proforma
**LIVER ENQUIRIES - Patient Considerations**

**Gathering the Information**

<table>
<thead>
<tr>
<th>Test</th>
<th>Range</th>
<th>Date</th>
<th>Date</th>
<th>Date</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>&lt;40 iu/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>&lt;40 iu/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alk Phos</td>
<td>30-300 iu/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bil</td>
<td>3-15 μmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alb</td>
<td>34-48 g/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGT</td>
<td>0-40 iu/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>0.9-1.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td>9-14.5 secs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creat</td>
<td>80-115 μmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Check enquirers range - ranges may vary, particularly Alk Phos

Do you have results of any tests?

**Ultra Sound Scan**

**Biopsy**

**ERCP/HIDA**

**Endoscopy**

Is there known Portal Hypertension

Does the patient have any other conditions or medications that need to be considered?

What is the liver diagnosis?

What is the ideal choice of agent(s)?

Over what timescale has this occurred?

Acute - could this be hepatotoxicity?

Chronic - Is the pt cirrhotic?

Any signs or symptoms?

Encephalopathy - present or previous

Jaundice or Pale stools/Dark urine

Ascites - present or previous

Varices - present or previous

**Applying the Information**

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

Key: A: Absorption  D: Distribution  M: Metabolism  E: Elimination  P: Pharmacodynamics
# LIVER ENQUIRIES - Drug Considerations

## Pharmacokinetics

<table>
<thead>
<tr>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
</tr>
<tr>
<td>Lipid solubility</td>
</tr>
<tr>
<td>(Absorption affected by ascites)</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
</tr>
<tr>
<td>Water/fat</td>
</tr>
<tr>
<td>Protein binding %</td>
</tr>
<tr>
<td>Displaced by bilirubin or</td>
</tr>
<tr>
<td>displaces bilirubin</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
</tr>
<tr>
<td>First pass effect</td>
</tr>
<tr>
<td>Hepatocyte dependent</td>
</tr>
<tr>
<td>Prodrug</td>
</tr>
<tr>
<td>CYPs</td>
</tr>
<tr>
<td>Active metabolites</td>
</tr>
<tr>
<td>Genetics</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
</tr>
<tr>
<td>Biliary excretion</td>
</tr>
<tr>
<td>Alternative mechanisms</td>
</tr>
<tr>
<td>Enterohepatic recirculation</td>
</tr>
<tr>
<td>(Renal impairment)</td>
</tr>
</tbody>
</table>

## Other Relevant Adverse Effects

- **Dermatological**
  - eg. pruritus and urticaria
  - What is the incidence of this reaction?
  - Is it a common, uncommon or rare effect?

- **Endocrine/Metabolic**
  - eg. fluid & electrolyte imbalance
  - What is the incidence of this reaction?
  - Is it a common, uncommon or rare effect?

- **Gastrointestinal**
  - eg. constipation
  - What is the incidence of this reaction?
  - Is it a common, uncommon or rare effect?

- **Haematological**
  - eg. Thrombocytopenia, effects on clotting, increased risk of bleeding
  - What is the incidence of this reaction?
  - Is it a common, uncommon or rare effect?

- **Neurological**
  - eg. confusion, seizures, sedation
  - What is the incidence of this reaction?
  - Is it a common, uncommon or rare effect?

## Adverse Effects:

### Hepatotoxicity

- Does the drug affect LFTs?
  - What is the incidence of this reaction?
  - Is this a transient effect?
  - Is it known how long it will take for the LFTs to recover?

- Is the drug associated with causing hepatitis or cholestasis?
  - What type of reaction does it cause?
  - What is the incidence of this reaction?
  - How long does it take to recover from this effect?

- Is the drug associated with any more serious or long-term hepatotoxic reactions?
  - eg hepatic necrosis, vanishing bile duct syndrome?
  - What is the incidence of this reaction?

### Renal

- eg. renal toxicity
  - What is the incidence of this reaction?
  - Is it a common, uncommon or rare effect?

### Are there any drug interactions or drug-disease interactions that need to be considered?
Why so much information?

- Back to 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
Plan for session

- Types of liver related MI enquiries
- Why it is so hard to answer them
- Basic hepatology
- Interpreting laboratory tests
- Pharmacokinetics and dynamics
- Pulling together an answer
Where is the liver?

- In a child it can be felt 1-2cm below the ribcage.
- In adults it can only be felt if it is enlarged.
- RUQ pain if enlarged.
What does the liver do?

- **Homeostasis**
  - e.g. glucose

- **Synthesis**
  - e.g. albumin & clotting factors

- **Metabolism**
  - e.g. drugs, oestrogens, toxic products such as ammonia

- **Lipid Metabolism**
  - e.g. cholesterol

- **Filtration**
  - e.g. antigens

- **Bile production and secretion**
Terminology – time frame

- **Acute**
  Sudden onset – jaundice to encephalopathy in less than 7 days (hyperacute), 28 days (acute), 6 months (sub-acute)

- **Chronic**
  Extended duration – months/years
Terminology – type of picture

- **Hepatocellular**
  - Fatty infiltration (steatosis) e.g. alcohol
  - Inflammation (hepatitis) e.g. viral
  - Cell death (necrosis) e.g. POD

- **Cholestasis**
  - Static bile flow (not specifically bilirubin)
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

  - **Decompensated cirrhosis**
    When a cirrhotic liver can no longer function adequately – signs eg coagulopathy occur
Portal hypertension
Terminology - Cholestasis

Intrahepatic

Extrahepatic
Causes of liver disease

- Metabolic & inherited – CF, Alagille, tyrosinaemia, Wilson’s
- Autoimmune – AIH, PSC, PBC
- Structural – biliary atresia, choledochal cysts
- Infection – hepatitis B, C
- Alcoholic liver disease
- Non-alcoholic fatty liver disease
- Cancer – usually underlying cirrhosis
Causes of liver dysfunction

- Ischaemia
- Infection – H1N1, CMV, EBV, malaria...
- MOF
- Drugs/TPN
- Trauma
- Oncological – metastases
- Gallstones, pancreatitis
Need to know:

- the type of dysfunction your patient has - hepatocellular or cholestatic
- the degree of dysfunction
Why?

Cholestasis
- Impaired elimination of biliary cleared drugs, malabsorption of fat soluble drugs

Hepatocellular damage
- Impaired metabolism, reduced protein binding, deranged distribution …
How?

Diagnosis

- Gallstones – cholestasis, normal hepatocyte function
- Tyrosinaemia – hepatocyte damage, normal bile flow
- Auto-immune hepatitis – hepatitis → fibrosis → cirrhosis → cholestasis → decompensated cirrhosis
Where on the continuum?

Diagnosis

Liver Test Results (and other tests)

Signs of Liver Disease

The patient
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)
- Also found in heart, muscle and kidney
- ALT more specific to liver than AST
Alkaline Phosphatase
(normal range varies for age and hospital)

- **Biliary enzyme** – raised with bile duct damage
  - Increased in cholestasis
- **Less raised in hepatocellular disease**
- **Not specific to the liver**
  - also found in bone (eg raised in Paget’s disease/bone metastases)
  - small quantities in the intestine and placenta
Gamma glutamyl transferase (GGT) (0-30u/l)

- Enzyme in biliary tract
  - Increased in cholestasis
- Increased by enzyme inducing drugs e.g. rifampicin and alcohol
- Useful to determine if isolated raised alkaline phosphatase is liver related
Bilirubin (3-17 micromol/l)

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

- **Conjugated**
  - Intrahepatic cholestasis
  - Extrahepatic cholestasis (gall stones, BA)
Albumin (37-49g/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
Prothrombin Time (~13 secs) or INR (0.9-1.2)

- Decreased synthesis of clotting factors (cirrhosis)
- Vitamin K malabsorption (in cholestasis)

- Elevation > 3 seconds significant
- Prolonged in acute & chronic liver disease
- Useful prognostic indicator of impending liver failure e.g. acute liver failure or decompensated chronic liver disease
Other useful tests

- Ultrasound – liver texture, dopplers for blood flow in hepatic artery, portal vein
- Liver biopsy – fibrosis, cirrhosis, intrahepatic cholestasis
- OGD – varices
- HIDA – bile flow (cholestasis)
- Blood glucose, creatinine
Signs of liver dysfunction

- Jaundice
- Pale stools/dark urine
- Palmar erythema
- White nails
- Gynaecomastia/testicular atrophy
- Spider naevi
- Ascites
- Bruising and bleeding
- Splenomegaly
- Oesophageal and gastric varices
- Encephalopathy
Symptoms of liver dysfunction

- Pruritus
- Lethargy
- Abdominal pain
- Bruising and bleeding
- Anorexia
### Problem with specificity

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Range</th>
<th>Possible Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>25</td>
<td>(5-40 u/l)</td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
<td>28</td>
<td>(5-17 μmoles/l)</td>
<td></td>
</tr>
<tr>
<td>1. Alk Phos</td>
<td>499</td>
<td>(30-300 u/l)</td>
<td>normal liver function; Pagets disease</td>
</tr>
<tr>
<td>2. Alk Phos</td>
<td>499</td>
<td>(30-300 u/l)</td>
<td>itch, liver biopsy; primary biliary cirrhosis</td>
</tr>
<tr>
<td>3. Albumin</td>
<td>21</td>
<td>(35-50 g/l)</td>
<td>normal liver function; malnourished</td>
</tr>
</tbody>
</table>
ALT 25 (5-40 u/l)
Bilirubin 28 (5-17 µmoles/l)

4. INR 1.9, prothrombin time 21 (12-16 sec)
   ⇒ normal liver function; on warfarin

5. Alk Phos 499 (30-300 u/l)
   Albumin 21 (35-50 g/l)
   INR 1.9 (PT 21 secs)
   ⇒ a. combination of any of above diagnoses
   ⇒ b. ascites, encephalopathy, varices;
      end stage chronic liver disease
Helps to decide how to modify drug therapy and to categorise patient into one of the following types:

- Hepatitis
- Cholestasis
- Cirrhosis – compensated
- Cirrhosis – decompensated
- Acute liver failure
LIVER ENQUIRIES - Patient Considerations

Gathering the Information

<table>
<thead>
<tr>
<th>LFT</th>
<th>Date</th>
<th>Date</th>
<th>Date</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT &lt;40iu/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST &lt;40iu/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alk Phos 30-300iu/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bil 3-15 µmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alb 34-48g/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGT 0-40iu/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR 0.9-1.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT 9-14.5 secs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creat 80-115 µmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Do you have results of any tests?

Ultra Sound Scan

Biopsy

ERCP/HIDA

Endoscopy

Is there known Portal Hypertension

Does the patient have any other conditions or medications that need to be considered?

Check enquirers range - ranges may vary, particularly Alk Phos

What is the liver diagnosis?

What is the ideal choice of agent(s)?

Over what timescale has this occurred?

Acute - could this be hepatotoxicity?

Chronic - Is the pt cirrhotic?

Any signs or symptoms?

Encephalopathy - present or previous

Jaundice or Pale stools/Dark urine

Ascites - present or previous

Varices - present or previous

Applying the Information

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/heporenal
Encephalopathy (P) | Cirrhosis

Key: A: Absorption  D: Distribution  M: Metabolism  E: Elimination  P: Pharmacodynamics
Next stage - drug

- PK
- PD
- ADRs
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
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
Decompensated cirrhosis - 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
Metabolism

- Prodrugs that need to be metabolised to the active form in the liver may need bigger doses! E.g. enalapril
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?
Pharmacodynamics

- Increased receptor sensitivity
  - More permeable BBB
  - Increased respiratory depression with opioids
Side Effect Profile

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

- GI ulceration – *varices, coagulopathy*
- Constipation – *cirrhosis, encephalopathy*
- Pruritus - *cholestasis*
- Sedation – *encephalopathy, cirrhosis*
- Coagulation defects - *coagulopathy*
- Effects on electrolytes – *cirrhosis, encephalopathy*
- Effects on fluid balance – *ascites, cirrhosis*
- Renal toxicity - *cirrhosis*
Hepatotoxicity

- Dose dependent (intrinsic e.g. paracetamol, methotrexate)
- Dose independent (idiosyncratic)
- Usually acute, can be chronic
- Acute is usually in 5 to 90 days of starting drug
- Can occur after stopping causative drug
- Existing liver dysfunction does not increase risk of hepatotoxic reaction
## LIVER ENQUIRIES - Drug Considerations

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Lipid solubility (Absorption affected by ascites)</td>
</tr>
<tr>
<td>Distribution</td>
<td>Water/fat Protein binding % Displaced by bilirubin or displaces bilirubin</td>
</tr>
<tr>
<td>Metabolism</td>
<td>First pass effect Hepatocyte dependent Prodrug CYPs Active metabolites Genetics</td>
</tr>
<tr>
<td>Elimination</td>
<td>Biliary excretion Alternative mechanisms Enterohepatic recirculation (Renal impairment)</td>
</tr>
</tbody>
</table>

### Other Relevant Adverse Effects

- **Dermatological**
  - eg. pruritus and urticaria
  - What is the incidence of this reaction?
  - Is it a common, uncommon or rare effect?

- **Endocrine/Metabolic**
  - eg. fluid & electrolyte imbalance
  - What is the incidence of this reaction?
  - Is it a common, uncommon or rare effect?

- **Gastrointestinal**
  - eg. constipation
  - What is the incidence of this reaction?
  - Is it a common, uncommon or rare effect?

- **Haematological**
  - eg. Thrombocytopenia, effects on clotting, increased risk of bleeding
  - What is the incidence of this reaction?
  - Is it a common, uncommon or rare effect?

- **Neurological**
  - eg. confusion, seizures, sedation
  - What is the incidence of this reaction?
  - Is it a common, uncommon or rare effect?

### Adverse Effects:

#### Hepatotoxicity

- Does the drug affect LFTs?
  - What is the incidence of this reaction?
  - Is this a transient effect?
  - Is it known how long it will take for the LFTs to recover?

- Is the drug associated with causing hepatitis or cholestasis?
  - What type of reaction does it cause?
  - What is the incidence of this reaction?
  - How long does it take to recover from this effect?

- Is the drug associated with any more serious or long-term hepatotoxic reactions?
  - eg hepatic necrosis, vanishing bile duct syndrome?
  - What is the incidence of this reaction?

- Are there any drug interactions or drug-disease interactions that need to be considered?
Key messages – when to worry

- Cirrhosis, esp decompensated – encephalopathy, coagulopathy
- Varices – risk of bleeding, effect on first pass metabolism
- Ascites – Na content, fluid retention
- Cholestasis – if drug biliary cleared
- Low albumin – if highly protein bound >90%
Drugs to avoid/use cautiously!!

- NSAIDs
- Opioids
- Tricyclic antidepressants
- Benzodiazepines
- Antipsychotics
- Antimuscarinics
- Anticholinergics
- Long acting drugs unless carefully titrated and pt stable
Which analgesic can you use in a patient with liver disease?

a) Paracetamol  
b) Ibuprofen  
c) Morphine  
d) Don’t know  
e) Need more information
### Review of common analgesics

#### Analgesia
- Paracetamol
- Ibuprofen
- Morphine

<table>
<thead>
<tr>
<th>Drug Considerations</th>
<th>Drug …………………</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetics</td>
<td></td>
</tr>
<tr>
<td>Absorption</td>
<td>Lipid solubility</td>
</tr>
<tr>
<td></td>
<td>(Absorption affected by ascites)</td>
</tr>
<tr>
<td>Distribution</td>
<td>Water/fat</td>
</tr>
<tr>
<td></td>
<td>Protein binding % Displaced by bilirubin or displaces bilirubin</td>
</tr>
<tr>
<td>Metabolism</td>
<td>First pass effect Hepatoocyte dependent Prodrug</td>
</tr>
<tr>
<td></td>
<td>CYPs</td>
</tr>
<tr>
<td></td>
<td>Active metabolites Genetics</td>
</tr>
<tr>
<td>Elimination</td>
<td>Biliary excretion Alternative mechanisms</td>
</tr>
<tr>
<td></td>
<td>Enterohepatic recirculation (Renal impairment)</td>
</tr>
</tbody>
</table>

#### 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

Published information in specific liver diseases/clinical studies
BNF/SPC
Effect of drug on liver patient

- Hepatitis
  - Mild, normal INR and no chronic liver disease
- Cholestasis
  - Normal hepatocyte function
- Cirrhosis
  - Compensated but only just – INR 1.3-1.4, albumin 32, known varices, no encephalopathy
Paracetamol

- Hepatic metabolism (multiple pathways)
  - Need glutathione – stores may be reduced in the severely malnourished
- Hepatotoxic in overdose

![Metabolism Diagram]

1. Paracetamol → oxidation via CYP2E1 → NAPQI
2. NAPQI → conjugation with glutathione → Mercapturic acid/Cysteine acid conjugates
3. Conjugation pathways:
   - Glucuronide
   - Sulphate
4. Conjugation with protein sulfhydryls → Complexes → Hepatotoxicity
Choice of analgesic? Paracetamol

- Use in mild hepatitis?
  - Yes  *(caution alcoholics)*

- In cholestasis?
  - Yes

- In cirrhosis?
  - Yes
  - Reduce to TDS in severe decompensated cirrhosis

- In acute liver failure?
  - Yes – possibly reduce to TDS
  - Not if cause of ALF is POD!
Choice of analgesics? 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
Choice of analgesic? Ibuprofen

- Use in mild hepatitis?
  - Yes – normal dose but monitor for hepatotoxicity
- In 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
- In cirrhosis?
  - Poor metabolism, accumulation
  - Bleeding risk, renal toxicity, fluid and electrolyte disturbance
  - AVOID
Morphine

- Low protein binding
- Extensive hepatic metabolism, first pass >50%
- Biliary excretion and enterohepatic recirculation
- Half life 1-5 hrs
- Side effects
  - Sedation, respiratory depression
  - Constipation
  - Pruritus
Morphine

- Use in mild hepatitis?
  - Yes – normal dose

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

- In cirrhosis?
  - Poor metabolism, accumulation. Varices may affect 1st pass
  - Sedation, resp depression – encephalopathy
  - Caution reduce dose (to 25-50%) and frequency
• Paracetamol is OK
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

Advise accordingly
Sources of further information

- Medicines Q&As on NELM
- Drug PK data – Dollery, micromedex, SPC
- Drugs and the Liver!

Caution with interpreting references
### Child-Pugh score – cirrhosis only

<table>
<thead>
<tr>
<th>Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBr</td>
<td>&lt;34</td>
<td>34-51</td>
<td>&gt;51</td>
</tr>
<tr>
<td>Albumin</td>
<td>&gt;35</td>
<td>30-35</td>
<td>&lt;30</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
<td>1.7-2.3</td>
<td>&gt;2.3</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Easily controlled</td>
<td>Poorly controlled</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Minimal</td>
<td>Advanced</td>
</tr>
</tbody>
</table>

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