Prescribing to Patients with Liver Diseases

Dr Grace Lai-Hung Wong
MBChB (Hons, CUHK), MD (CUHK), MRCP, FHKCP, FHKAM (Medicine)

Associate Professor
Center for Liver Health & Institute of Digestive Disease
The Chinese University of Hong Kong

What you want to know when prescribing to patients with liver diseases

• Effect of the diseased liver on the drugs

• Effect of drugs on the diseased liver

• Put together:
  – Can this drug be used?
  – Any precautions?
  – What dosage?
Liver – primary site of drug metabolism

Liver biochemistry

Drug characteristics e.g. pharmacokinetics, side effects

Signs of liver diseases
**Impaired drug handling in liver diseases**

- Reduced absorption edematous GI tract in ascites
- Reduced absorption in cholestasis
- Liver cell necrosis
- Shunting of the blood through porto-systemic colaterals
- Reduction in drug-binding proteins
- Abnormal drug volume distribution
- Altered drug elimination
- Altered drug metabolism
- Altered pharmaco-dynamics
- Associated renal failure
- Drug-drug interaction

**Side effect profiles – special precautions**

- Ulcerogenic
- Coagulopathy
- Sedative
- Effects on electrolytes
- Effects on fluid balance
- Renal toxicity
Drugs to avoided or used with caution

• NSAID / anticoagulations – variceal or ulcer bleeding
• Sedatives – hepatic encephalopathy
• Opiate – constipation and hepatic encephalopathy
• Diuretics – electrolytes disturbance and hepatic encephalopathy

Prescribing in liver diseases – practical issues

• Pharmacokinetic changes are not predictable
• Liver has amazing capacity even when cirrhotic
• Be careful not to under dose patients for essential therapies e.g. chemotherapy
Rule of thumb when prescribing in liver diseases

- Avoid or use certain drugs cautiously
- Avoid hepatotoxic drugs if possible
- Use therapeutic levels whenever possible
- Monitor for efficacy e.g. BP, heart rate
- Monitor for toxicity
- Check renal function
- Start with smallest effective dose and titrate accordingly

Liver diseases and drug induced liver injury
Two conditions seldom overlap
In most cases, risk of hepatotoxicity is not increased when a drug is used in a patient with liver disease.

But outcome can be worsen

The same degree of liver injury, which is well tolerated in a normal subject, can trigger liver failure, complications and death in patients with an already impaired liver function.

Agents with increased risk of hepatotoxicity in patients with chronic liver diseases

- Rifampin, INH, pyrazinamide (In HBV & ETOH patients)
- Antiretrovirals (In HCV & HBV patients)
- Methotrexate (in alcoholic & NAFLD)
- Niacin (sustained-release formulation)
- Antiandrogens (flutamide)
- Valproic acid
- Methimazole
- Vitamin A (in large doses)

Zimmerman HJ: Hepatotoxicity. The Adverse Effect of Drugs and Other Chemicals on the Liver. Lippincott Williams & Wilkins, Philadelphia. 1999
Effect of drugs on the diseased liver

• It is safe to prescribe most medications in patients with liver diseases.

• Just pay special attentions to some agents with increased risk of hepatotoxicity in chronic liver diseases.

Zimmerman HJ: Hepatotoxicity. The Adverse Effect of Drugs and Other Chemicals on the Liver. Lippincott Williams & Wilkins, Philadelphia

Rules for Detecting Hepatotoxicity

• ALT elevation
  – <3x ULN no action needed
  – >3x ULN deserves close attention
  – >5x ULN discontinue the medication

• Hy’s Law
  – ALT + bilirubin elevation = disaster!

Reuben A, Hepatology 2004;39:574-578
Hy’s rule
by late Hyman Zimmerman 1914-1999

- If both drug-induced hepatocellular injury and jaundice occur at the same time without biliary obstruction, mortality of at least 10% can be expected
- ALT 3xULN and bilirubin 2xULN
- Advocated by FDA as an assessment tool of hepatotoxicity of new drugs

ALT monitoring – useful or useless?

<table>
<thead>
<tr>
<th>Frequent</th>
<th>Infrequent</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Weeks</td>
<td>4 Weeks</td>
</tr>
<tr>
<td>ALAT &gt; 5 ULN → Stop treatment → No jaundice</td>
<td></td>
</tr>
</tbody>
</table>

Infrequent

Frequent
Frequent monitoring in high risk cases, OR

Rather than infrequent LFT monitoring, it’s best to

**WARN THE PATIENT**

“Consult and have liver tests performed if you don’t feel well”

“Stop treatment immediately should you become jaundiced”

Common examples of using hepatotoxic drugs in liver diseases
Can you prescribe a statin?

- **Yes!**

- **Dallas Heart Study**
  - Statin use:
    - No increased prevalence of elevated ALT
    - No worsening hepatic steatosis

- **Histopathological study**
  - Statin use:
    - Significant reduction in liver fat
    - Reduced progression to advanced fibrosis

---

Statins in patients with elevated liver enzymes

### Predominantly NAFLD patients

<table>
<thead>
<tr>
<th></th>
<th>Patients With Normal Enzymes Who Took Statins (n = 1417)</th>
<th>Patients With Elevated Enzymes Who Did Not Take Statins (n = 2245)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-moderate elevations in liver biochemistries*</td>
<td>1.7%</td>
<td>4.7%</td>
</tr>
<tr>
<td></td>
<td>( P = .002 )</td>
<td>( P = .2 )</td>
</tr>
<tr>
<td>Severe elevations in liver biochemistries*</td>
<td>0.2%</td>
<td>0.6%</td>
</tr>
<tr>
<td></td>
<td>( P = .6 )</td>
<td>( P = .6 )</td>
</tr>
</tbody>
</table>

---

1. Browning JD. Hepatology 2006;44:466-471

High Dose Pravastatin in Liver Disease Patients

Similar results for
-- Baseline normal vs. elevated ALT
-- HCV vs. NAFLD patients

Analgesics in liver disease

• Paracetamol
  – Safe in small quantities
  – Probably the safest analgesic for liver patients
  – Reduce maximum daily intake and avoid regular dosing for >5 days)
    • ie 500mg QID prn (max 2g daily)
Metabolism of paracetamol

- **Paracetamol**
- **Glucuronide and Sulphate conjugates** (60-90%)
- **Cytochrome P450** (5-10%)
- **Reactive metabolite**
- **Hepatocyte damage**
- **Glutathione**
- **Excretion**

**Enhanced activity**
- Enzyme inducers
- Alcohol

**Depletion in Malnutrition**
- N-acetylcysteine
- Methionine

**Replenish stores**
- Methionine

**Lower treatment threshold in chronic liver diseases**
Analgesics in chronic liver disease

- NSAIDs
  - NEVER! Variceal haemorrhage, renal failure

- Codeine/Tramadol
  - Risk of encephalopathy
  - Need to balance risk versus need for analgesia
  - Co-prescribe lactulose
  - Use lower doses, avoid regular dosing

- Stronger opiate
  - Never without consultation with specialist
  - High risk of over-sedation and encephalopathy
  - Effects may be delayed/prolonged

TB Treatment and Liver Disease

- Use standard short-course regimen for patients without clinical evidence of chronic liver disease but history of:
  - Viral hepatitis (acute or chronic)
  - Excessive alcohol consumption

- Use a liver-sparing regimen for patients with established chronic liver disease
  - 2SHRE/6HR or 2SHE/10 HE
TB Treatment and Hepatitis

• Asymptomatic elevation ALT occurs in 20% patients on 4 drugs
• Drug induced hepatitis = ↑ ALT ≥3xULN with symptoms OR ↑ >5 times if asymptomatic
• INH, PZA and RIF can all cause hepatotoxicity
  – INH: age related
  – PZA: dose related
  – RIF: unpredictable and less common

TB Treatment and Hepatitis - Management

• If ↑ ≥3x normal with symptoms or >5x normal without symptoms:
  – stop all anti-TB medications and evaluate patient
  – try to rule out other causes of acute liver disease
  – if severely ill, may start 3 non-hepatotoxic drugs
  – after ALT <2xULN — rechallenge drugs one-by-one starting with drugs that are not hepatotoxic
Antibiotics to be avoided in liver diseases

- Chloramphenicol—higher risk of bone marrow suppression (markedly increased half life)
- Erythromycin estolate: causes cholestasis
- Tetracycline—dose related hepatotoxicity
- Griseofulvin—contraindicated
- Nitrofurantoin prolonged use

Antibiotics to be used with cautions

- Piperacillin
- Ceftazidime
- Ceftriaxone
- Cefoperazone +/- Sulbactam
- Erythromycin
- Azithromycin
- Tetracycline
- Cotrimoxazole + Trimethoprim
- Metronidazole
- Ketoconazole & other fluconozoles
Conclusions

- Most drugs are safe in liver diseases
- Use certain drugs cautiously
- Avoid hepatotoxic drugs if possible (or close monitoring if deem necessary)
- Immediate stop suspected drugs with deteriorated LFT (hopefully before development of jaundice)