Pharmacology in Liver Disease

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Objectives

• Outline the drug management for patients with:
  – Ascites
  – Spontaneous Bacterial Peritonitis (SBP)
  – Encephalopathy
  – Bleeding varices
  – Hepatorenal syndrome
  – Pruritus
  – Alcohol withdrawal

• Describe the factors which need to be considered when selecting drugs and dosage regimens in chronic liver disease.
Ascites

- Treatment aim - mobilisation of intra-abdominal fluid
- No added salt diet (80mmol/day)
- Diuretics
- Fluid restriction to 1.5-2L/day
  - (if serum sodium <130mmol/l)
- 90% of patients can be managed as above
- Paracentesis
- TIPSS (transjugular intrahepatic portosystemic shunt)
Drug Choices - Diuretics

- Aldosterone antagonist:
  - Spironolactone 100-400mg od
  - Increased aldosterone due to activation & reduced degradation by liver

  Plus/minus

- Loop diuretic:
  - Frusemide (40-160mg od)
  - Bumetanide (1-4mg od)
Diuretics - side effects

- Hyperkalaemia (spironolactone)
- Hypokalaemia (loop diuretics)
- Hyponatraemia (stop if Na <120mmol/L)
- Nephrotoxicity
- Gynaecomastia (Spironolactone)
- Encephalopathy (electrolyte disturbances)
Monitoring

• Daily weight
  – aim to lose 0.5kg/day or 1-2kg/day if peripheral oedema

• Dose titrate every 3-5 days

• U&Es
  – Renal function (creatinine, urea)
  – Na, K
Spontaneous Bacterial Peritonitis

- Start antibiotics whilst awaiting the results of culture of ascitic fluid
  - eg. Piperacillin Tazobactam IV 4.8g 8 hourly (some centres use Cefuroxime, Ciprofloxacin)

- Treat for 5 days - when clinically improved

- Long term prophylaxis
  - Previous episodes of SBP
  - Ascitic protein <10g/l
    = Co-Trimoxazole 960mg OD
Encephalopathy

• Treatment aim: to improve cognitive function

• Events precipitating hepatic encephalopathy:
  – Infection
  – Bleeding e.g. GI
  – Electrolyte imbalance
  – Constipation
  – Drugs
  – Acute liver failure
  – Porto-systemic shunts
• Identify & treat precipitating factors

• Remove causative drugs:
  – Sedating e.g. benzodiazepines
  – Constipating e.g. opioids
  – Diuretics – electrolyte imbalance
Treatment

• Lactulose 10-50ml bd-tds
  – Laxative effect
  – Broken down in gut leading to acidification of colonic contents and a reduction in absorption of nitrogenous waste

• Side effects of lactulose
  – Flatulence
  – Abdominal pain
  – Diarrhoea

• Enemas
  – If NBM
Antibiotics for Encephalopathy

• **Rifaximin 550mg BD**
  – broad antimicrobial spectrum against most of the Gram-positive and negative, aerobic and anaerobic bacteria, including ammonia producing species
  – reducing the production of ammonia and other compounds that are believed to be important to the pathogenesis of hepatic encephalopathy.

• **Side effects**
  – Nausea
  – Anaemia
  – Ascites
  – Peripheral Oedema
Monitoring

- **Stool chart**
  - Aim to produce 2-3 loose stools a day

- **Temperature if infection**

- **Cognitive improvement**
  - Number connection tests
  - Serial sevens
Bleeding Varices

Aims of Treatment
- Resuscitate (blood/FFP/colloids)
- Control bleeding (medical & endoscopic treatment)
- Prevent complications
- Prevent re-bleeding

Stop bleeding
- Drug therapy: Terlipressin, Octreotide

Plus 1 of:
- Sclerotherapy
- Endoscopic Oesophageal Banding
- Adhesives e.g. Histoacryl glue for gastric varices
- TIPSS (transjugular intrahepatic portosystemic shunt)
Octreotide & Terlipressin

- Reduce portal pressure by causing splanchnic vasoconstriction
- Reduce re-bleeding rates

- Terlipressin (reduced mortality)
  - 1-2mg IV bolus 4-6 hourly (usually 2mg qds)
- Octreotide (unlicensed use)
  - Continuous IV infusion - 50mcg/hour

- Usually discontinued 2 days after bleeding stopped (terlipressin licensed for 72 hrs)
Terlipressin side effects

- Abdominal cramps
- Headache
- Increased blood pressure
Monitoring: Terlipressin/Octreotide

- Bleeding
- Blood Pressure
- Length of treatment course
Antibiotics in Variceal Bleed

• Reduce bacteraemia: SBP
• Reduce short term mortality
• Local policy
  – Piperacillin-Tazobactam 4.5g IV for 48 hours
Prevention of recurrent variceal bleeding

- Non-selective beta-blockers e.g. Propranolol or Nadolol
  - Reduce portal pressure by decreasing splanchnic blood flow and the hyperdynamic circulation associated with cirrhosis
  - Starting dose: propranolol 20-40mg bd up to 80mg bd
  - Reduce mortality
Beta blocker side effects

- Bronchospasm (Cl in asthma)
- Bradycardia
- Hypotension
- Peripheral vasoconstriction
- Fatigue
- Impotence
Beta blocker monitoring

- BP
  - Aim for >100mmHg systolic (some patients may tolerate lower)

- Heart rate
  - Aim of treatment is to reduce HR to 25% less than baseline (above 55bpm) - this is the maximum tolerated dose
Hepatorenal Syndrome (HRS)

- Renal impairment associated with liver disease
- Low arterial pressure, reduced renal perfusion
- Aim to increase renal perfusion and renal function
- Vasoconstrictors constrict splanchnic bed and increase renal perfusion
- Poor prognosis
Treatment of HRS

- Terlipressin IV used most frequently
  - Unlicensed use
  - Range of doses in studies from 0.5mg bd to 2mg 6 times a day
  - In practice, St James’s liver unit use 1mg qds
  - In combination with 20% HAS

**Remove any nephrotoxic medications**
Pruritus in liver disease

- Cause?
- Subjective; varies from patient to patient
- Can be all over body, in eyes, ears etc or isolated areas
- Often worse at night and when hot
- Can be debilitating
- Can be indication for liver transplant
- Efficacy of treatment can be monitored by visual analogue scale
Pruritis – Treatment options

• Topical preparations
  – E.g. menthol 1% in aqueous cream
  – Do not apply on broken skin
  – Short term, immediate relief
  – May not be useful for patients with generalised all over itch

• Antihistamines
  – non-sedating (e.g. cetirizine) - ? ineffective
  – sedating (e.g. chlorpheniramine)
  – Sedating drugs can be useful at night to aid sleep
Cholestyramine (Questran®)

- Anion exchange resin; forms insoluble complexes with bile acids in the intestine and excreted in faeces (prevents their absorption).
- Initiate at 4g od or bd
- May take 48 hours to take effect
- Reduces absorption of other drugs - give other drugs 1 hour before or 4-6 hours after colestyramine
- Can mix in drinks / incorporate into recipes
Cholestyramine side effects

• Not absorbed therefore no systemic side effects:
• Unpleasant taste
• Constipation
• Occasionally, diarrhoea
• Nausea & vomiting
• Can cause depletion of fat soluble vitamins long term
Ursodeoxycholic acid

- Naturally occurring bile acid; displaces toxic bile acids from enterohepatic pool, protects cells from toxic bile acids and stimulates bile excretion.
  - “displacement theory”
- Dose: 10-15mg/kg/day
- Can be given in divided doses or single dose
- Can take up to 2 weeks to take effect
- May worsen itch!
Other options for Pruritis

- **Rifampicin / Phenobarbitone**
- Induce hepatic enzymes
- Not licensed for this indication
- Rifampicin 150mg bd, increase to 300mg bd
- Takes 48 to 72 hours to work
- Interacts with lots of drugs (not ideal post transplant)
- Colours urine red
- Ondansetron
- Not licensed for this indication
- 5HT3 antagonist
- Inhibits perception of itch
- Anecdotal reports suggest IV has been effective (within 1 hour)
- If effective after stat IV dose, give oral 4mg bd increasing to 8mg bd
• **Opioid antagonists;** Work quickly but patients become tolerant, therefore regular dose increases necessary
  – Naloxone – continuous infusion
  – Naltrexone orally 25-50mg daily

• **Serotonin Selective Reuptake Inhibitors eg** Sertraline

• **Gabapentin**
Alcohol Withdrawal

- Anxiety, tremor, sweating, nausea, tachycardia, hypertension, hallucinations

- Chlordiazepoxide (regular and prn)
  - Initially chlordiazepoxide ~20-30mg qds + 5-10 mg prn
  - A maximum daily dose of 120mg
  - Reducing course over ~ 7 days
Wernicke’s encephalopathy

- Vitamin B deficiency
- Thiamine -100mg tds
- Vitamin B Co. strong - 2 tabs tds
- High risk
  - Pabrinex IV 1 pair Daily for 3-5 days
  - Anaphylaxis risk – give over >10mins
- Treatment (1 or more signs present)
  - Pabrinex IV 2 pairs tds for 2 days followed by 1 pair twice a day until improvement ceases
• How to determine a patient’s liver function and how it effects drug handling……

• There isn’t a book that gives dosing of drugs in liver impairment

• No way of measuring directly the liver’s ability to metabolise drugs

• Effects of liver impairment on the way drugs are handled in the body not consistent & predictable

• Limited published information available (which maybe misleading e.g. from manufacturers)
References

• “Drugs and the Liver”
• A guide to drug handling in liver dysfunction
• Edited by Penny North-Lewis
  – Paediatric Liver Pharmacist, SJUH
Need to consider lots of factors.....

- LFTs
- Clotting function
- Signs
- Diagnosis
- Other investigations e.g. biopsy, ultrasound
- The drug
Drug handling in particular patient

Liver Test Results

Drug Characteristics
- e.g. how drug is handled in body and side effects

Signs of Liver Disease

The patient
The drug

- Absorption
- Distribution
- Metabolism
- Elimination
- Side Effect profile
- Hepatotoxicity
Absorption of some drugs may be affected by oedema in ascites (e.g. frusemide? - less absorption in gut wall)

Fat soluble drugs have reduced absorption in cholestasis (e.g. fat soluble vitamins)

The effect of fat soluble drugs may be increased in Cachetic patients
Distribution

- Fat soluble drugs are not affected by ascites

- Water soluble drugs will distribute into ascitic fluid which may lead to lower serum concentration and reduce efficacy
  - May need to increase dose
Distribution

- Reduced albumin levels
  - If highly protein bound drug (ie binds to albumin);
    Increased free drug available = toxic
  
  - E.g phenytoin (90%), warfarin (99%)

**May need to reduce dose**
Metabolism

• Reduced number of hepatocytes may lead to reduced metabolism of drugs (to active/ inactive form)

• Reduced hepatic flow in portal hypertension/ cirrhosis leads to increased systemic availability (reduced first pass metabolism)
• Accumulation may occur in cholestatic patients if the drug undergoes biliary excretion

  – a problem if active/toxic metabolites are produced
  – alternative routes of elimination? e.g. kidneys
Side Effect Profile

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

- Sedation
- Constipation
- Coagulopathy
- Effects on electrolytes
- Effects on fluid balance
- Renal toxicity
- GI ulceration
Drugs to avoid/use cautiously

- **NSAIDs/ Anticoagulants**
  - In cirrhotics – risk of varices/bleeding abnormalities

- **Sedatives**
  - In cirrhotics/encephalopathics – sedatives mask/precipitate encephalopathy.

- **Constipating drugs**
  - Risk of encephalopathy with constipation

- **Diuretics**
  - Electrolyte imbalance can precipitate encephalopathy

- **Sodium containing drugs e.g. IV or effervescent preparations**
  - May worsen ascites
Important Points to Consider

- Avoid or use certain drugs cautiously
- Avoid hepatotoxic drugs if possible
- Use therapeutic levels, where possible
- Monitor for efficacy eg BP, HR
- Monitor for toxicity
- Check renal function
- Use the smallest effective dose at the greatest interval and titrate according to response
- Take Care: not to under dose!
Drug Choice in liver disease

• Analgesics
  ➢ Paracetamol – normal doses
  ➢ Opiates – small doses, titrate slowly – care with constipation/sedation (encephalopathy)

• Antidepressants
  ➢ SSRI’s e.g. Fluoxetine, venlafaxine over older sedating drugs e.g. amitriptyline (tricyclic antidepressant)

• Anti-emetics
  ➢ Ondasetron

• Benzodiazepines
  ➢ Short acting
Any Questions?