# PHA-6020

Patient centred medicine from bench to bedside

## Workshop

# Liver disease

### Learning Outcomes

By the end of this workshop you will be able to:

- Critique and make recommendations for the treatment of a patient with chronic alcoholic liver disease
- Advise on the therapeutic and toxic monitoring parameters for a patient with chronic alcoholic liver disease
- Rationalise the use of common medicines used in patients with liver cirrhosis

## Pre-workshop tasks:

- Listen to liver screencasts (independent study for week 1 semester 2)

## Resources

You will need to refer to the following documents to complete this workshop:

- NNUH Trust guideline for the management of: Acute Alcohol withdrawal (excluding pregnancy). Please view online.
- Summary document of common drugs known to cause liver disease.

**Patient case 1**

**You have a new patient on your ward. His medical notes and blood test results are below:**

| | | |
|---|---|---|
| | **Patient:** | *Mr AM* |
| | **Hospital number:** | *555999* |
| | **DoB:** | *28/12/1970* |
| | **Address:** | *18 Hills Road, Flatplace* |
| **Allergies:** | *NKDA* | |
| **Weight:** | *98kg* | |
| **Occupation:** | *Unemployed* | |
| **Alcohol:** | *currently approximately 20 units/day* | |
| **Smoking status:** | *Non-smoker* | |
| **MHx:** | *Chronic Alcohol Related liver disease (Feb 2021)*<br>*Patient not been attending planned outpatient appointments.* | |
| **DHx:** | *Nil regular medicines* | |
| **PC:** | *Confusion* | |
| **HPC:** | *Found in his garden in the middle of the night by his neighbour.*<br>*Neighbour reports him acting very strangely and not making much sense when talking.* | |
| **OE:** | *Patient smelt strongly of alcohol.*<br>*Dishevelled appearance.* | |
| | BP: | *145/82 mmHg* |
| | Temperature: | *37.4 degrees Celsius* |
| | Pulse: | 92 *BPM* |
| | *Spider naevi on face and abdomen.*<br>*Mild jaundice to skin and eyes.*<br>*Palmer erythema.*<br>*Grossly distended abdomen.*<br>*Urinary frequency.*<br>*Bilateral pitting oedema.* | |
| **Δ** | Acute alcohol withdrawal with progression to liver cirrhosis | |

| **PATHOLOGY DEPARTMENT** | | Consultant/GP: Dr J Henderson | | PATIENT LOCATION **PATH** |
|---|---|---|---|---|
| Patient Name: AM | | | NHS No: 49746 | |
| Hosp no: *555999* | DOB: 28/12/70 | Sex: M | Age: 53Y | Pathology |
| Patient Address: 12 Primrose Lane, Flat Place | | | | |
| Lab Episode No: | 1671 | | Date/Time Collection: 31/1/2023 | |
| Address for Report: Flat Place Hospital, Flat Place | | | | |

| BIOCHEMISTRY<br>Collection 31/01/2023<br>LAB No 1671 | Total protein<br>**51*** (60-80) g/dl | Albumin<br>**27*** (35-50) g/dl | Bilirubin<br>**65*** (3-20) µmol/l | ALP<br>**370*** (20-100) IU/l | AST<br>**212*** (5-40) IU/l |
|---|---|---|---|---|---|
| | ALT<br>**60*** (5-30) IU/l | GGT<br>**246*** (5-45) IU/l | PT<br>**22*** (10-15) secs | Hb<br>**9.9*** (14-18) g/dl | WBC<br>10.3 (4-11) x $10^9$/l |
| | Na<br>134 (134-145) mmol/L | K<br>4.7 (3.6-5.0) mmol/L | Urea<br>6.8 (1.7-7.1) mmol/L | Creatinine<br>123 (55-125) µmol/L | |

No result for ammonia. Would expect urea to decrease as it is not produced by the liver and ammonia to rise as it is what the liver converts to urea. This leads to encephalopathy as ammonia crosses the BBB. Some patients do not have increased ammonia but display symptoms of HE – there is believed to be other mechanisms by which HE occurs, i.e. increased permeability of the BBB.

**1. What signs/symptoms and lab test results are consistent with alcoholic liver disease?**

| **Sign/symptom/blood test result** | **Brief description of pathophysiology behind the result/presentation seen for the patient** |
|---|---|
| **Medical history** – continued excessive alcohol intake.<br><br>Signs/symptoms:<br>• **confusion** [⇒ alcohol withdrawal/ encephalopathy/W-K syndrome], | Alcohol withdrawal – minor - CNS hyperactivity (insomnia, tremor, anxiety, diaphoresis, palpitations).<br>Seizures.<br>Delirium tremens (DTs) – hallucinations, confusion, disorientation, tachypnoea, hypertension, agitation, severe tremor, diaphoresis – can be fatal. |

| | |
|---|---|
| | Encephalopathy can be due to ammonia crossing the BBB, as it cannot be broken down to urea in the liver and due to the disrupted blood flow through the liver meaning it enters the systemic circulation.<br><br>Wernicke-Korsakoff syndrome. This is a neurological syndrome due to the deficiency of vitamin B (thiamine) due to malnutrition. |
| • **jaundice** [impaired metabolism],<br><br>(When thinking about some of the symptoms of liver disease we need to consider their causes. The liver receives ~75% of its blood from the hepatic portal vein which drains the capillary bed of the gut, arterial blood comes from the hepatic artery. Normally large volumes of blood flow through the liver uninterrupted however in many liver diseases, vascular resistance is increased due to inflammatory damage (fibrosis) with the formation of some new blood vessels. This can further develop to cause disrupted architecture loss of function and random, disordered regeneration of the hepatocytes and of circulation. This leads to increased portal vein hypertension ⇒ formation of collateral circulation (smaller thin-walled veins and the formation of new, disorganised thin walled vessels) and other symptoms of the disease…) | Impaired liver cannot effectively conjugate and excrete bilirubin therefore it is increased in the circulation and appears in the skin and in the sclera of the eyes. |

| | |
|---|---|
| • distended abdomen [⇒ **ascites**], | Number of causes. Activation of renin/ang/aldesterone system due to the reduced renal blood flow seen when there is the disordered anatomy of the hepatic/collateral blood flow. This leads to retained sodium and water. Secondary hyperaldosteronism – due to this activation. This means that there is fluid retention and is exaggerated as the liver would normally metabolise aldosterone which cannot happen as liver failing.<br>Reduced albumin – reduces the osmotic pressure in the plasma and causes leakage and oedema/accumulation in tissues – peritoneal cavity. Due to the portal hypertension, this accumulation occurs around the abdomen. |
| • **spider naevi**, | Due to the vascular changes as described above. Dilation of vessels on the skin. Usually found on the torso. Can be seen in other situations pregnancy/COC use. |
| • **palmer erythema**, | Due to the altered circulation. |
| • **peripheral oedema**, | As above<br><br>(What is another symptom of the collateral system? - Bleeding oesophageal varices.) |
| Blood tests:<br>• ↑ Bil,ALP [⇒ ↓ bilary secretion], | Alk phos - v. high in biliary obstruction and also found in other tissue.<br><br>Bili – jaundice (yellowing of skin) when >35 micromol/L. |
| • ↑ ALT, AST, GGT [⇒ liver cell damage], | Transaminases – AST in hepatocytes and other tissue not just liver. ALT more specific to liver. Seen in cholestatic jaundice and cirrhosis.<br>Ratio AST/ALT>2 alcohol injury, <1 other disease.<br><br>GGT very high in biliary obstruction and lower increases in alcohol/drug tox/hepatitis/cirrhosis/cholestatis. Also, in other tissue. |

| | |
|---|---|
| | Elevated when patients drink but reduce after 3-6 weeks of abstinence-good for monitoring adherence.<br><br>Where enzymes are found in other tissue LFTs must be interpreted with the whole patient picture – MHx, signs etc. |
| • ↓ albumin [is the liver working?], | Albumin made only by liver, 20-26 day half life means reductions are indicative of long term damage. |
| • ↑ PT [⇒ ↓ function] [is the liver working?], | How long it takes for the blood to clot. It is increased when there is a lack of underlying clotting factors. Depends on factor 2, 7, 9 and 10, increasing if these factors are not produced. These require vitamin K (fat soluble vitamin needing bile salts for absorption) – administration of vit K can indicate the type of damage there is, i.e. give Vit K no response = hepatocellular damage as it is not able to produce the clotting factors, whereas, if the issue is cholestasis where there is a deficiency in bile salts (needed to absorb vit K) the PT will decrease. |
| • ↓ Hb [aneamia/bleeding] | Bone marrow suppression in end stage disease. |
| Electrolyte abnormalities | May appear low as dilutional effect of excessive fluid intake. |

What would your thoughts be if the patient had signs of liver disease but LFTs are not raised?

- Severe liver impairment, there are not the hepatocytes present to produce the enzymes and so may appear to be normal.

Mr AM was confused and disorientated, he was extremely agitated, had a marked tremor and was feeling sick at admission.

**Mr AM's drug chart can be seen below:**

## UEA Training Prescription Chart

Number of drug charts in use: 1

| Date | Surname | Forename | Sex | D/O/B | Hosptial No. | Weight (kg) | Height (cm) | Surface Area ($m^2$) | SAM? |
|---|---|---|---|---|---|---|---|---|---|
| **Day 1** | **M** | **A** | M | 28/12/1970 | 555999 | 98 Estimate / **Actual** | | | Yes / **No** |

| | | | |
|---|---|---|---|
| **Ward/ward change:** | **Hepatology** | **Patient address:** | **18 Hills Road, Flatplace** |
| **Consultant(s)** | **AN Doctor** | | |

**DRUG SENSITIVITIES/ALLERGIES MUST BE ENTERED.** If no allergies/sensitivites you must write 'NKDA' and sign and date.

| Medicine/Substance | Description of allergy/sensitivity | Signature | Date |
|---|---|---|---|
| *NKDA* | | *S. Kenny* | *Day 1* |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

**PRE-MEDICATION AND ONCE ONLY DRUGS**

| Pharm | Date | Drug (approved name) | Dose | Directions/ route/ other | Time to be given | Signature | Administered by | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Initials | Date |
| | **Day 1** | *Diazepam* | **10mg** | **PO STAT** | **1am** | *AN Doctor* | **KL** | **Day 1** |
| | | | | | | | | |
| | | | | | | | | |

**Thromboprophylaxis Risk Assessment**

| | |
|---|---|
| Drug thromboprophyaxis recommended | |
| Drug thromboprophlaxis NOT recommende | **X** |

### Prescribing

- Write clearly in black, indelible ink.
- Use approved drug names.
- All prescriptions must be signed and dated.
- If a drug is to be intentionally omitted by a prescriber or pharmacist, indicate this with an 'X' in the drug administration box.
- If a drug is being stopped, or a dose altered, draw a line through the whole prescription, sign and date.
- Doctors to re-write charts as required. Start dates should be transferred to new chart. Include cross-reference to drugs on other charts.

### Drug omissions

If a drug is omitted, one of the below codes must be entered into the drug administration box.

1. Nil by mouth
2. Not required
3. Patient refused
4. Drug unavailable
5. Vomiting/nausea
6. Patient off ward
7. No IV access
9. Contra-indicated
8. Other - reason must be recorded in notes

### Self administration of medicines (SAM)

**If** a patient is suitable for SAM they can initial in the relevant drug administration box or a nurse can write 'SAM' in the box.

### Prescribers

| | |
|---|---|
| Signature | *AN Doctor* |
| Bleep no. | **5893** |
| Print name | **AN Doctor** |
| Signature | ***Dr Jones*** |
| Bleep no. | **3210** |
| Print name | **KE Jones** |
| Signature | |
| Bleep no. | |
| Print name | |
| Signature | |
| Bleep no. | |
| Print name | |
| Signature | |
| Bleep no. | |
| Print name | |

### Pharmacy codes

Pharm: Signature confirms checked/date

**TTO** ✓ = from locker; **H** = at home; **R** = relabel; ✱ = new supply at discharge

## REGULAR MEDICINES 1

CHECK PAGE 1 FOR ALLERGY STATUS

| Date → / Tick box to indicate time of admission or add other times ↓ | | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Day 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Drug (approved name): Lactulose; Start date: Day 1; End date: | 06:00 | | | | | | | | | | |
| | 08:00 | ✓ | HJ | | | | | | | | |
| Dose: 5mL; Route: PO; Frequency: BD | 12:00 | | | | | | | | | | |
| | 14:00 | | | | | | | | | | |
| Indication: | 18:00 | | | | | | | | | | |
| Pharm check: | 22:00 | ✓ | | | | | | | | | |
| Prescriber's signature: AN Doctor; Supply: | 00:00 | | | | | | | | | | |
| 2. Drug (approved name): Pabrinex HP; Start date: Day 1; End date: | 06:00 | | | | | | | | | | |
| | 08:00 | ✓ | HJ | | | | | | | | |
| Dose: 1 pair; Route: IV; Frequency: OD | 12:00 | | | | | | | | | | |
| | 14:00 | | | | | | | | | | |
| Indication: | 18:00 | | | | | | | | | | |
| Pharm check: | 22:00 | | | | | | | | | | |
| Prescriber's signature: AN Doctor; Supply: | 00:00 | | | | | | | | | | |
| 3. Drug (approved name): Vitamin K; Start date: Day 1; End date: Day 5 | 06:00 | | | | | | | | | | |
| | 08:00 | ✓ | HJ | | | X | X | X | X | X | X | X |
| Dose: 10mg; Route: im; Frequency: OD | 12:00 | | | | | | | | | | |
| | 14:00 | | | | | | | | | | |
| Indication: Phytomenadione | 18:00 | | | | | | | | | | |
| Pharm check: | 22:00 | | | | | | | | | | |
| Prescriber's signature: AN Doctor; Supply: | 00:00 | | | | | | | | | | |
| 4. Drug (approved name): Spironolactone; Start date: Day 2; End date: | 06:00 | | | | | | | | | | |
| | 08:00 | ✓ | X | | | | | | | | |
| Dose: 100 mg; Route: PO; Frequency: OD | 12:00 | | | | | | | | | | |
| | 14:00 | | | | | | | | | | |
| Indication: | 18:00 | | | | | | | | | | |
| Pharm check: | 22:00 | | | | | | | | | | |
| Prescriber's signature: AN Doctor; Supply: | 00:00 | | | | | | | | | | |
| 5. Drug (approved name): Start date: End date: | 06:00 | | | | | | | | | | |
| | 08:00 | | | | | | | | | | |
| Dose: Route: Frequency: | 12:00 | | | | | | | | | | |
| | 14:00 | | | | | | | | | | |
| Indication: | 18:00 | | | | | | | | | | |
| Pharm check: | 22:00 | | | | | | | | | | |
| Prescriber's signature: Supply: | 00:00 | | | | | | | | | | |

CHECK PAGE 1 FOR ALLERGY STATUS

## AS REQUIRED DRUGS

CHECK PAGE 1 FOR ALLERGY STATUS

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Drug (approved name) | | Start date | Date | | | | | | | | | | | |
| Dose | Route | Max Frequency | Time | | | | | | | | | | | |
| Indication | | Pharm check | Dose | | | | | | | | | | | |
| | | | Route | | | | | | | | | | | |
| Prescriber's signature | Supply | | Given by | | | | | | | | | | | |
| 2. Drug (approved name) | | Start date | Date | | | | | | | | | | | |
| Dose | Route | Max Frequency | Time | | | | | | | | | | | |
| Indication | | Pharm check | Dose | | | | | | | | | | | |
| | | | Route | | | | | | | | | | | |
| Prescriber's signature | Supply | | Given by | | | | | | | | | | | |
| 3. Drug (approved name) | | Start date | Date | | | | | | | | | | | |
| Dose | Route | Max Frequency | Time | | | | | | | | | | | |
| Indication | | Pharm check | Dose | | | | | | | | | | | |
| | | | Route | | | | | | | | | | | |
| Prescriber's signature | Supply | | Given by | | | | | | | | | | | |
| 4. Drug (approved name) | | Start date | Date | | | | | | | | | | | |
| Dose | Route | Max Frequency | Time | | | | | | | | | | | |
| Indication | | Pharm check | Dose | | | | | | | | | | | |
| | | | Route | | | | | | | | | | | |
| Prescriber's signature | Supply | | Given by | | | | | | | | | | | |
| 5. Drug (approved name) | | Start date | Date | | | | | | | | | | | |
| Dose | Route | Max Frequency | Time | | | | | | | | | | | |
| Indication | | Pharm check | Dose | | | | | | | | | | | |
| | | | Route | | | | | | | | | | | |
| Prescriber's signature | Supply | | Given by | | | | | | | | | | | |

CHECK PAGE 1 FOR ALLERGY STATUS

**2. Comment on the choice of 'once only' medication used to control the agitation, tremor and nausea. Explain what alternative recommendations you would make to the junior doctor?**

Symptoms highly likely to be due to alcohol withdrawal – anxiety, agitation, sweating, hypertension, tremor, tachycardia, restlessness, insomnia, N&V, confusion.

Regularly drinking 15 units/day and or a score of >15 on the Severity of Alcohol Dependence Questionnaire SADQ (appendix 2) tells us how likely they are to get withdrawal and predict severity. This can be used to determine doses of treatment.

Healthcare professionals can use the clinical Institute Withdrawal Assessment of Alcohol Scale – CIWA-Ar (Appendix 1) to help determine when a dose of benzodiazepine.

Treatment is symptom control (benzo) and supportive care - correct fluid and electrolyte abnormalities.

Benzodiazepines – control psychomotor agitation and prevent progression to more severe adverse effects.

Diazepam is a benzodiazepine.

However, diazepam long acting [half-life 20-100hr] + ↑ risk of masking encephalopathy. It is also prone to abuse.

In acute alcohol withdrawal syndrome recommend a reducing regime of chlordiazepoxide. This is also a long acting benzodiazepine and is more effective than shorter acting ones at preventing seizures and delirium. They have less rebound than shorter acting agents. Chlordiazepoxide has a more gradual onset of psychotropic effects, less potential for misuse and less toxic in overdose.

There is an accumulation risk in elderly and those with liver failure. Shorter acting agents such as oxazepam [half-life about 3-21hrs] can be used. **Therefore, for this patient oxazepam would be best however will require close observation to avoid withdrawal symptoms.**

You want to use the lowest possible dose without causing sedation as this increase's likelihood of encephalopathy.

See separate oxazepam prescription and NNUH guidance on the doses that are given. Some patients as a standard regime whereas other (where specially trained staff are available to monitor the patient) a symptom triggered regime may be used. This involves reviewing the patient for symptoms and giving doses if necessary using the clinical Institute Withdrawal Assessment of Alcohol Scale – CIWA-Ar (Appendix 1).

Fixed dose chlordiazepoxide could therefore be between 20-40mg QDS starting dose and then decreased over 9-10 days.

**Due to the hepatic impairment in this patient the symptom triggered approach is preferred and the use of the dose.**

Do not send home with supply – issue of dependence and risk of respiratory depression (especially when used with alcohol).

3. **For each of the remaining drugs on the drug chart (and any recommendations you make in question 2):**
   - **Comment on their appropriateness,**
   - **Identify any pharmaceutical care issues,**
   - **Describe the actions you would need to take to manage/resolve the issue,**
   - **List appropriate therapeutic and toxic monitoring parameters.**

| **Drug:** Lactulose | |
|---|---|
| **Appropriateness:** Appropriate treatment of hepatic encephalopathy [↓ pH of intestine & therefore ↓ ammonia-forming bacteria, reduction in absorption of the now ionised molecules, ↑ gut transit time & therefore ammonia absorption].<br><br>Other options - Rifaximin (added when optimised lactulose not working) and phosphate enema. | |
| **Issues** | **Action required** |
| Dose potentially too low as signs of HE. Must check stool chart/assess stool frequency/consistency. | Speak to Dr to get dose amended to achieve 2-3 loose stools per day [up to 50ml tds]. Likely to be too low a starting dose – start 20ml bd-tds to 30-50mL TDS.<br><br>Ensure avoidance of precipitating factors – dehydration, hypokalaemia, GI haemorrhage, CNS drugs, high protein diet, constipation. |
| **Monitoring parameters** | |
| **Therapeutic** | **Toxic** |
| Symptoms of encephalopathy,<br>stool chart (aim 2-3 loose stools per day) | Stool chart - avoid diarrhoea causing dehydration/hypovolaemia<br>Adherence<br>s/e abdo pain, flatulence, N&V |

| **Drug:** Pabrinex IVHP (vit B and C given over 30 mins) | |
|---|---|
| **Appropriateness:** B vitamins are appropriate for use in a patient with alcoholic liver disease as alcoholism is associated with vitamin B1 deficiency which can lead to Wernicke's encephalopathy and Korsakoff's psychosis (Wernicke-Korsakoff syndrome).<br>IV form, dose dependent on likelihood of the syndrome. | |
| **Issues** | **Action required** |
| Risk of anaphylaxis with IV pabrinex.<br><br>Dose potentially too low. | Speak to Dr regarding a dose change considering probable withdrawal and risk of WKS. As per NNUH guidelines – 2 pairs TDS for 3 to 5 days. |

| | |
|---|---|
| | Alongside oral thiamine 100mg TDS, continued for 3-6 after abstinence is achieved or long-term if drinking continues. |
| **Monitoring parameters** | |
| **Therapeutic** | **Toxic** |
| No signs/symptoms of WKS | Anaphylaxis<br>Injection site reactions |

| | |
|---|---|
| **Drug:** Vitamin K injection (phytomenadione) | |
| **Appropriateness:** As clotting factors are made in the liver; impairment may mean that these are not produced and increase a patient's risk of bleeding. Mr AM's prothrombin time is elevated.<br>In patients with alcoholic liver disease, which increases their risk of major bleeds such as oesophageal varices, you want to reduce the risk of bleeding wherever possible. This may not work if their liver damage is extensive as it is due to a lack of liver production of clotting factors and not a lack of vitK absorption.<br>IM – not appropriate as it increases the risk of bleeding and haematoma formation. | |
| **Issues** | **Action required** |
| Method of administration not appropriate. It increases the risk of bruising and bleeding in a patient already at increased risk of this. | Ask dr to prescribe IV.<br><br>Ensure avoidance of aspirin/NSAID and anticoagulants |
| **Monitoring parameters** | |
| **Therapeutic** | **Toxic** |
| Prothrombin time – reducing to normal | Method of administration |

| | |
|---|---|
| **Drug:** Spironolactone 100mg od | |
| **Appropriateness:** First line treatment for ascites (add in furosemide if desired effect of optimised spiro not seen and if other areas of oedema). To get rid of the accumulated fluid. It is an aldosterone antagonist and as this is part of the cause, it means it is a first line choice.<br>Fluid restriction.<br>Paracentesis. | |
| **Issues** | **Action required** |
| None - appropriate choice & starting dose for treatment of ascites | |
| **Monitoring parameters** | |
| **Therapeutic** | **Toxic** |
| weight loss [aim 0.5-0.75 kg/day or 1-1.5 kg/day if peripheral oedema] needs to | U&E's [RF and K+/Na+]<br>gynaecomastia |

| | |
|---|---|
| be steady to prevent hypovolaemia and reduced K+ and Na+,<br><br>abdominal girth | s/e |

4. **Document any additional pharmaceutical care issues and actions in the table below, [including any additional drug therapy that should be considered]?**

| Issues | Action required |
|---|---|
| Continuation of thiamine to reduce the risk of V-K syndrome | Ensure supply of thiamine 100mg TDS for discharge. |
| Referral to DAL to help with dependence on alcohol. | Refer to DAL team. |
| Multivitamins – due to potential malnutrition. | |
| To reduce the risk of bleeding from the collateral circulation we should aim to reduce the portal blood pressure using low dose – carvedolol or propranolol (cautiously titrated as drug undergoes extensive first pass metabolism so need to monitor effect in a liver patient). | Check whether the medical team are thinking of initiating (carvedolol 6.25 mg) or propranolol (40mg BD) adjust according to HR. |

The next day, the junior doctor asks for your advice on the diuretic therapy. Mr AM has not lost enough weight since he was admitted and asks how he should increase the spironolactone.

5. **What advice would you give the junior doctor?**

Spironolactone takes 2-3 days to have effect, therefore continue for at least another day.
If desired reduction in weight/girth not seen, ↑ by 100mg every 2 days until diuresis achieved [max 600mg per day, although in practice doses this high rarely used – single dose or divided if causes GI side-effects]

Add in furosemide if still no weight loss [especially if also peripheral oedema].

Caution not to cause hypovolaemia due to risks associated with encephalopathy.

6. **What other drugs should the doctor and Mr AM be recommended to avoid or use with caution due to his liver cirrhosis? Why?**

You need to consider which function of the liver have been lost in your patient. For the patient in this workshop with cirrhosis, they have lost their metabolic, excretory

and synthetic capabilities. Therefore, careful consideration is required for any drug that relies on these properties.

- **Hepatotoxic** – see separate sheet for details of the types of hepatoxicity some drugs can cause.

- **Anything affecting clotting/bleeding** eg. NSAIDs, warfarin, DOACs, clopidogrel, heparin, corticosteroids SSRI's (increased risk of upper GI bleeding and decreased serotonin uptake into platelets reducing their ability to form clots )– patient is likely to have clotting abnormalities (reduction in clotting factor production, and splenomegaly causing low red cells, white cells and platelets). Portal hypertension can cause splenomegaly and therefore low counts – increased bleed risk, and development of a collateral circulation in delicate blood vessels of the oesophagus and stomach which can rupture and cause excessive bleeding – risk with drugs causing GI bleeding.
- **Anything causing GI ulceration** e.g. NSAIDs, corticosteroids, aspirin, bisphosphonates.

Why are NSAIDs particularly problematic?
– GI irritation and GI bleeding, sodium and water retention.

- **Anything that affects CNS** e.g. opioids, tricyclic antidepressants, sedating antihistamines, benzodiazepines and other hypnotics, antipsychotics – use with caution in those at risk of developing encephalopathy. Responsiveness to the pharmacological action of some drugs may lead to increased susceptibility of the brain. If the metabolic capacity of the liver is impaired (acute liver failure of cirrhosis) a patient is at risk of becoming encephalopathic or of worsening encephalopathy. The brain is more sensitive to the sedative effects of any drug due to increased permeability of the BBB, cerebral blood flow and receptor sensitivity. The CNS side effects, sedation and confusion, can increase the risk or worsen the grade of encephalopathy by compounding the CNS depressant effects. Decreased metabolism also increases the risk of this happening.

What are your views on modified release opioid analgesia?
- Not ideal due to long period to wear off that can mask the adverse effects for longer. If deterioration is noted in the patient, you cannot do much about it until the drug has worn off (unless you reverse the analgesia with naloxone).

- Most opioids are metabolised in the liver and have a high intrinsic clearance/high first pass effect, therefore when metabolism is impaired, or blood flow is reduced (for high extraction ratio drugs), clearance of the opioid is decreased resulting in prolonged duration and toxicity. Portal hypertension (and increased systemic exposure) may increase oral bioavailability and toxicity risk. Therefore, it is difficult to predict pharmacokinetics.

- Paracetamol – data is conflicting regarding the safety in liver disease and dosing will be guided by local policy. Theoretically liver enzyme induction (by chronic alcohol or enzyme inducing drugs) may enhance the production of toxic metabolites. Caution is necessary in patients that cannot eliminate the toxic metabolite due to decreased glutathione, i.e. malnourished patients. In practice we reduce the dose in patients less than 50 kg, malnourished and those with liver disease to 500mg QDS or TDS or 15 mg/Kg.

- **Over diuresis and electrolyte abnormalities** e.g. high dose furosemide, bumetanide (inappropriate starting doses and/or titration). These drugs will disturb the fluid-electrolyte balance which can lead to encephalopathy in susceptible (cirrhotic or acute failure patients), i.e. dehydration, hyponatraemia, hyper or hypokalaemia.

- **Drugs that lower the seizure threshold** e.g. tramadol, phenothiazine antipsychotics and some antidepressants. These may accumulate due to cirrhosis or acute liver failure and are particularly problematic in alcoholic patients who have an increased risk of seizure due to alcohol withdrawal.

- **Causing constipation** e.g. opioid analgesics, tricyclic antidepressants, sedating antihistamines, 5HT3 antagonists, calcium channel blockers, antispasmodics-hyoscine, antimuscarinics-Parkinsons drugs. Constipation prevents the clearance of toxic waste products in the bowel that can accumulate and cross the BBB to cause or worsen HE

- **Highly protein bound drugs** i.e. phenytoin, ibuprofen, prednisolone, verapamil are unable to bind plasma proteins and albumin therefore increasing the free drug.

- **High sodium content drugs**, especially an issue with IV preparations and soluble tablets. These can cause fluid retention and worsen ascites.

- **Nephrotoxic drugs** – patients with cirrhosis or acute liver failure are at risk of hepatorenal disease and are also more susceptible to renal impairment than those without renal impairment.

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