Anesthesia and Liver Disease

What liver functions are relevant to anesthesia?

- Protein homeostasis
    - Albumin synthesis
        - Oncotic pressure and fluid balance
        - Drug binding
            - Hypoalbuminemia and increased active, free fraction
            - Effect is worse for highly-bound drugs
                - Alfaxalone is normally 50% protein bound. If albumin is 50% of normal, the free fraction increases 1.5 fold (75% free)
                - Propofol is 98% protein bound. If albumin is 50% of normal, the free fraction increases 25 fold (51% free)
                - This is simplified but suggests that the dose needs to be adjusted much more for propofol than alfaxalone
        - Clotting factors
        - Esterases
- Drug Metabolism
    - Most drugs are metabolized by CYP450 in the liver
        - Some drugs directly eliminated
        - Other organs contribute to metabolism of some drugs
        - Some drugs metabolized by plasma and/or ubiquitous tissue enzymes
        - Phase I reactions (oxidation, reduction, hydrolysis)
        - Phase II reactions (conjugation)
            - Cats are deficient in both
        - Severe liver disease may compromise these reactions
    - Factors influencing drug metabolism
        - Liver blood flow
        - Induction
        - Competition
        - Inhibition
        - Protein binding
            - Only the free fraction can be metabolized
- Glucose homeostasis
    - Liver is responsible for maintaining normal glycemia
        - Glycogenolysis
        - Glycogenesis
        - Gluconeogenesis

Effects of Anesthetic Drugs

- All drugs that decrease cardiac output likely decrease liver blood flow
    - Alpha-2 agonists
    - Propofol
    - Alfaxalone(?)
    - Ketamine (only if no sympathetic response)
    - Inhalants
- Decrease their own metabolism, and that of drugs administered concurrently
    - Especially drugs with a high extraction ratio
- Anesthetic drugs may cause liver damage or dysfunction
    - Direct effect on hepatocytes
    - Effect on liver blood flow
    - Accumulation of hormones
    - Immune reactions (inhalants; very rare)
- Effect is likely small for isoflurane and sevoflurane
- Effect is greater with ketamine than with other injectable agents
- Acute fulminant hepatic necrosis in cats and oral diazepam
- NSAIDS may cause hepatitis
- Benzodiazepines and hepatic encephalopathy
    - Flumazenil (benzodiazepine antagonist) reduces signs in humans
    - Benzodiazepines may increase clinical signs of hepatic encephalopathy
- Sphincter on hepatic veins
    - Contract in response to
        - Decrease in sinusoidal pressure
        - Norepinephrine, angiotensin, hepatic nerve stimulation
        - Histamine (dogs)
            - Caution with histamine releasing drugs
                - Morphine, meperidine
                - Atracurium

Effects of Anesthesia and Surgery

- Systemic blood pressure
    - Liver blood flow is somewhat autoregulated
        - Mostly arterial blood flow
        - Only contributes approximately 50% of DO_2
    - Stimulation of alpha-1 adrenergic receptors
        - Decreases arterial blood flow to liver
        - Stress, catecholamines
        - Surgery

    - Mechanical ventilation
        - Decreases venous blood flow to liver
    - Hypoxemia
        - Decreases arterial blood flow to liver

Impact of a diseased liver

- Pharmacology of anesthetic drugs
    - Changes in response to given concentration
        - Hepatic encephalopathy and sensitivity to anesthetic drugs
    - Volume of distribution
        - Ascites may increase volume of distribution
    - Protein binding
        - Hypoalbuminemia and free (active) drug fraction for highly protein-bound drugs
    - Biotransformation/clearance
    - Phase I is more affected than phase II
        - Oxidation, reduction, hydrolysis
    - Affected drugs: Phenothiazines, benzodiazepines, opioids, etomidate, ketamine, local anesthetics
    - Drugs less affected/not affected: Propofol, isoflurane, sevoflurane, atracurium
    - Alfaxalone
        - Rapidly metabolized by the liver
        - Likely affected
    - Alterations in the blood-brain barrier
    - Response to anesthetic drugs +/- unpredictable
    - Importance of selection/titration

Anesthetic Management

- Clinical Signs
    - Depression
    - Anorexia
    - Diarrhea
    - Fever
    - CNS signs
    - Vomiting
    - Ascites
    - Icterus
- Hepatopathy and liver dysfunction are NOT synonymous
- Hepatopathy is largely irrelevant to anesthetic management
- Tests

    - Specific: Bile Acids
    - Screening: BUN, glucose, albumin, cholesterol
- Preanesthetic management
    - History: Drugs, vomiting
    - Physical exam: Hydration ascites
    - Blood work: electrolytes, glucose, proteins, COP, coagulation panel, PCV
- Consider crossmatch if liver surgery
- Primary goal is to maintain liver DO_2
    - Cannot directly measure
    - Rely on good bp and oxygenation
- Select drugs that are independent of liver function for clearance or that are reversible
    - Not all drugs with these characteristics are beneficial
    - Ex: Dexmedetomidine can be antagonized but would decrease cardiac output and liver DO_2
- Consider regional anesthesia to reduce the need for systemic drugs
- Carefully titrate to effect
- Fluid therapy: consider colloids/FFP if hypoalbuminemic
- Monitoring directed towards identification of hypoxemia and hypotension
- Maintain body temperature

Anesthetic plan

- Premedication
    - Patient is often depressed
    - Opioid (morphine, meperidine)
    - Anticholinergic?
- Induction
    - Preoxygenate
    - Inhalant
    - Propofol or etomidate
    - Avoid benzodiazepines, particularly if hepatic encephalopathy!
- Maintenance
    - Isoflurane or sevoflurane
    - +/- opioid CRI
        - Use lower doses, expect longer effects, consider reversal
    - Remifentanil
        - Metabolized by blood and tissue esterases
        - Tissue esterases are not produced in the liver

Support and monitoring

- 2 large bore catheters if liver surgery
    - Higher risk for hemorrhage
    - Have whole blood of PRBCs available
- ECG, Doppler BP, temperature probe
- Art line, ABG, PCV, TP, Glucose
- Pulse oximeter, capnograph
- IPPV as needed
- FFP +/- LRS +/- Blood products
- Active warming
- Blood pressure support
    - Fluids
    - Anesthetic technique
    - Dopamine
- Recovery
    - Analgesics
    - Fluid therapy +/- dextrose

Summary

Distinguish between hepatopathy and liver dysfunction, a hepatopathy without liver dysfunction has little anesthetic relevance. Look at the liver function parameters (Albumin, BUN, Bilirubin, Cholesterol, Glucose)

Maintain good liver blood flow, maintain good oxygenation and systemic hemodynamics

Select drugs that do not rely intensively on liver function for metabolism/excretion and/or are reversible and/or for which prolonged effects would not be too concerning

AVOID: Acepromazine, alpha-2 agonists, benzodiazepines (if hepatic encephalopathy) and ketamine

Opioids are our first choice (if possible, no morphine or meperidine in dogs), propofol, etomidate, inhalants are fine and alfaxalone is probably fine