Dose Considerations in Hepatic Disease

Specific Liver diseases

1. **Acute viral hepatitis:**

- **Changes in drug disposition are less pronounced than in chronic liver disease.**
- **Acute viral hepatitis has marginal effect on CYP2D6 activity, and its substrates can be given at regular doses.**

2. **Chronic hepatitis:**

- **The impact on drug metabolism is greater for phase I (oxidation) than phase II reactions (conjugation).**

Specific Liver diseases

- Some CYP enzymes are more affected than others.
- In chronic hepatitis without cirrhosis, rates of drug elimination are either similar or less than that in healthy subjects, but greater than patients with cirrhosis.
- Glucuronidation in liver disease is relatively spared, but NOT for all drugs.

Specific Liver diseases

3. **Cholestasis:**

- **Associated with reduction of CYP enzymes.**

<u>Plasma Protein Binding:</u>

- **Adjustment of phenytoin concentration in hypoalbuminemia:**
- $C_{normal} = C_{observed} / [0.2 (albumin) + 0.1]$

Select Drugs with Significantly Decreased Metabolism in Chronic Liver Disease

Caffeine	Chlordiazepoxide
Cefoperazone	Chloramphenicol
Diazepam	Erythromycin
Hexobarbital	Metronidazole
Lidocaine	Pethidine (meperidine)
Metoprolol	Tocainide
Propranolol	Verapamil
Theophylline	

Liver diseases

- **Hepatic disease can alter the pharmacokinetics of drugs including absorption and disposition; and pharmacodynamics including efficacy and safety.**
- **Drugs are often metabolized by one or more enzymes located in cellular membranes in different parts of the liver.**
- **Drugs and metabolites may also be excreted by biliary excretion.**

Liver diseases

- **Hepatic disease may lead to:**

a. **drug accumulation**
b. **failure to form an active or inactive metabolite**
c. **increased bioavailability after oral administration**
d. **changes in drug–protein binding.**

- **<u>Liver disease may affect kidney function</u>, which can lead to accumulation of a drug and/or its metabolites even when the liver is NOT primarily responsible for elimination.**

Liver diseases

- In contrast to creatinine clearance which has been used successfully to measure kidney function and renal clearance of drugs, there is NO such test to estimate hepatic clearance in patients with hepatic disease.
- Liver disease affects the quantitative and qualitative synthesis of albumin, globulins, and other circulating plasma proteins that might affect plasma drug protein binding and distribution.

Liver diseases

- **Drugs with flow-dependent clearance should be avoided if possible in patients with liver failure.**
- **Doses of such drugs may need to be reduced to as low as one-tenth of the conventional dose, for an orally administered agent.**
- **Starting therapy with low doses and monitoring response or plasma levels provides the best opportunity for safe, effective treatment.**

Active Drug and Its Active Metabolite

1. **When the drug is more potent than the metabolite, the overall pharmacologic activity will increase in the hepatic-impaired patient because the parent drug concentration will be higher.**
2. **When the drug is less potent than the metabolite, the overall pharmacologic activity in the hepatic patient will decrease because less of the active metabolite is formed.**

Assessment of Severity of Liver disease

Child-Turcotte-Pugh (CTP) classification of the severity of cirrhosis

	Points*		
	1	2	3
Encephalopathy	None	Grade 1-2 (or precipitant-induced)	Grade 3-4 (or chronic)
Ascites	None	Mild/Moderate (diuretic-responsive)	Severe (diuretic-refractory)
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
PT (sec prolonged) or INR	<4 <1.7	4-6 1.7-2.3	>6 >2.3

CTP score is obtained by adding the score for each parameter

CTP class: A = 5-6 points
B = 7-9 points
C = 10-15 points

Dose Considerations in Hepatic Disease

- Patients with hepatic cirrhosis are ~ 2-5 times more prone to adverse drug reactions than patients without hepatic dysfunction.
- This might be due to pharmacodynamic than pharmacokinetic changes.
- Little information is available on pharmacodynamic changes.
- Central nervous system sensitivity is increased for morphine, chlorpromazine, and diazepam.

Dose Considerations in Hepatic Disease

- **Hepatic encephalopathy can be precipitated by sedatives, analgesics and tranquilizers; and much more so by diuretics.**
- **Changes in pharmacologic activity due to hepatic disease may be much more complex when both the pharmacokinetic parameters and the pharmacodynamics of the drug change as a result of the disease process.**

Recommendations for select drug dosage change in patients with chronic liver disease.

Drug	Metabolism	Recommendation
Acetaminophen (Paracetamol)	Conjugation	Do NOT Exceed 2g/day
Allopurinol	Oxidation (active metabolite	Reduce dose 50%
Amitriptyline	Oxidation, conjugation	Start at 50% of normal dose, then adjust and monitor for clinical & adverse effect
Amlodipine	Extensive oxidation	Precaution
Azathioprine	Oxidation	Precaution

Carbamazepine	Oxidation, active metabolite, glucuronidation	Avoid, it worsen liver disease
Clindamycin	Extensive oxidation, active metabolite	Prolong dosing interval, monitor hepatic function
Clomipramine	Oxidation, glucuronidation	Avoid
Codeine	Extensive oxidation, active metabolite (morphine)	Avoid
Cyclophosphamide	Hydroxylation	Reduce dose 25%, monitor hepatic function

Cyclosporine	Oxidation to several metabolites	Precaution, measure drug level in whole blood
Dacarbazine	Extensive oxidation, toxic metabolites	Reduce dose 25-50%, monitor serum level
Daunorubicin	Cytotoxic metabolites, conjugation	Reduce dose 25-50%
Diazepam	Extensive oxidation, active metabolites	Reduce dose 50%, or use lorazepam
Doxycycline	Metabolized	Precaution, use other antibiotics
Enalpril	Active metabolites	Precaution

Erythromycin	Extensive oxidation	Reduce dose 30-50 %, Prolong interval to 8 hours
Fluoxetine	Oxidation, active metabolites	Reduce dose 50%
Fluphenazine	Oxidation, conjugation	Avoid
Glibenclamide	Extensive metabolism	Start with 1.25 mg and monitor effect
Ibuprofen	Extensive metabolism	Precaution
Isoniazid	Extensive metabolism	Contraindicated
Itraconazole	Extensive metabolism	Precaution
Lidocaine	Extensive metabolism	Avoid
Mefloquine	Extensive metabolism	Avoid

Metformin	No metabolism	Avoid
Methotrexate	Little metabolism	Avoid, contraindicated
Methyldopa	Metabolized 50%	Precaution
Metronidazole	Metabolized 50%, oxidation	250 mg/8hours
Morphine	Glucuronidation	Avoid
Phenytoin	Oxidation, glucuronidation	Increases liver toxicity, monitor, avoid
Phenobarbital	Oxidation, glucuronidation	Avoid
Pyrazinamide	Metabolized 95%	Precaution, monitor liver function, avoid

Rifampin	Liver metabolism, active metabolites	Max. dose 6-8mg/kg twice a week
Simvastatin	Extensive oxidation	Precaution
Trimethoprim/ sulfametoxazole	Oxidation, acetylation	Precaution
Valproic acid	Extensive oxidation, glucuronidation	Reduce dose 50%, monitor serum level
Verapamil	Extensive oxidation	Reduce 50% IV dose, and 20% oral dose
Vinblastine, vincristine	Extensive oxidation, biliary excretion	Reduce dose 50%
Voriconazole	Extensive oxidation	Reduce dose, prolong interval, or avoid
Warfarin	Extensive oxidation	Monitor INR