

DRUG USE IN LIVER IMPAIRMENT

Drugs that are predominantly hepatically cleared may require dosage adjustment in the presence of significant liver impairment. This bulletin discusses the general principles of the assessment of liver impairment with respect to drug metabolism, and the subsequent adjustment of drug doses.

There is no easily available measure of liver function, with the "liver function tests" such as AST, ALT, GGT & alkaline phosphatase providing an indication of liver cell damage rather than ability of the liver to metabolise drugs. This contrasts with renal disease, where estimates of renal function based on creatinine clearance correlate with renal drug elimination.

ASSESSMENT OF LIVER IMPAIRMENT

The best indices of impaired hepatic metabolic capacity are a low albumin concentration and raised prothrombin ratio (or INR). These reflect the capability of the liver to synthesise proteins and therefore the ability to synthesise drug metabolising enzymes. However, these markers may be influenced by other conditions, such as poor nutritional state, are only indicative of severe, chronic dysfunction and are not sensitive to rapid changes.

In the absence of other clinical explanations, severe liver dysfunction is indicated by an:

- ◆ albumin concentration of <30g/L, or
- ◆ INR of >1.2

Impaired metabolism is more predictable in the presence of chronic liver disease, although acute liver dysfunction is also associated with impaired capacity for drug metabolism.

HEPATIC DRUG CLEARANCE

Hepatic drug clearance is a function of liver blood flow (since the greater the blood flow, the greater the amount of drug that is presented to the liver for metabolism) and the intrinsic enzyme metabolising capacity of the liver for that drug. The hepatic extraction ratio is the fraction of drug removed from the blood in one passage through the liver.

High Clearance Drugs

The hepatic elimination of drugs with a high extraction ratio (eg. drugs with a high first-pass metabolism) is limited by both blood flow and enzyme capacity. As a large proportion of the drug is removed in one pass of the liver, the degree of removal is dependent on the delivery of drug to the liver by hepatic blood flow.

Low Clearance Drugs

Drugs with a low extraction ratio have a more limited capacity to be cleared. The presentation of more drug (ie. through increased blood flow) will not increase elimination further. Such drugs are less susceptible to alterations in liver function.

HEPATIC METABOLISM

There are two types of metabolic processes involved in the hepatic elimination of drugs. Phase I reactions involve enzymes belonging to the cytochrome P450 family and include hydrolysis, oxidation, dealkylation and reduction of the drug molecule. Phase II reactions involve conjugation of the drug molecule (or metabolite) to an endogenous molecule such as glucuronic acid, sulphate, amino acid, acetate or glutathione. This increases the water solubility of the drug to aid renal excretion.

In liver disease, impairment in drug metabolism may occur through decreased metabolizing enzyme capacity, decreased liver blood flow and intra/extra hepatic shunting. Prediction of

drug pharmacokinetics in the presence of hepatic impairment therefore relies on knowledge of the total drug clearance from the body (CL) and the extent of hepatic extraction.

Liver disorders that decrease drug metabolism include cirrhosis, alcoholic liver disease (chronic alcohol consumption may also increase drug metabolism via enzyme induction), viral hepatitis (may increase or decrease metabolism) and porphyria. Cirrhosis, porphyria and hepatoma do not appear to significantly alter hepatic glucuronidation and drugs solely eliminated via this mechanism are less likely to be affected (eg. morphine, lorazepam), than drugs that are not glucuronidated.

DOSING IN LIVER DISEASE

The recommendations below are somewhat arbitrary, but form a guide for dose adjustment in the presence of liver disease.

1. If unsure whether a drug is metabolised or renally cleared, check the drug profiles in the back of the PML ("pink book").
2. Decide on the appropriate daily dose for a patient with normal liver function.
3. For **severe** liver dysfunction (albumin<30g/L, INR > 1.2):
 - (a) If the drug is a **high clearance** drug (liver blood flow-dependent) ® **reduce dose by 50%:**

High Clearance Drugs:

Antipsychotics	Opioids (most)
Beta-blockers (most)	SSRIs
Calcium channel blockers	Statins
Lignocaine	Tricyclic antidepressants
Nitrates	

- (b) If the drug is **low clearance** (flow-independent - includes all other metabolised drugs)
® **reduce dose by 25%:**

Low Clearance Drugs: (examples)

Amiodarone	Quinidine
Anticonvulsants (most)	Retinoids
Antimalarials	Rifampicin
Antiparkinsons (except amantadine)	Spiroglactone
Antithyroid	Steroids
Benzodiazepines	Sulphonylureas
NSAIDs	Theophylline
Proton pump inhibitors	Warfarin
Paracetamol	

Low therapeutic index drugs require extra caution. Exact dosage adjustment is less critical for drugs with a wide therapeutic index.

When selecting drugs, choose those that are renally eliminated where practical (eg. atenolol rather than metoprolol). Alternatively, change to a drug that is glucuronidated rather than oxidised (eg. lorazepam rather than diazepam), as glucuronidation is less likely to be affected by hepatic disease. Avoid inherently hepatotoxic drugs (eg. carbamazepine, methotrexate).