# Drugs and the liver

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## Abstract

The liver is a major organ with multiple functions. A number of drugs are metabolized by the liver during phase 1 and 2 reactions which include complex processes involving cytochrome P450 enzymes. Genetic and acquired variability in cytochrome P450 activity may have profound effects on pharmacokinetics. Additionally, drugs can also modify how the liver functions and cause dysfunction or even failure of the organ both by a direct effect on the liver or by alteration in liver blood flow. It is important to recognize the signs and symptoms of liver failure in patients and identify possible causes including drug interactions. Furthermore, once a patient has been recognized to be suffering with liver dysfunction or failure drug choice and dosing regime will need to be rationalized. Paracetamol overdose can have severe and life-threatening consequences for patients due to its effect on liver function. It is the leading cause of acute liver failure in the UK. Correct and early management is crucial and will be discussed within this article.

**Keywords** Cytochrome P450; hepatic failure; liver; metabolism; paracetamol overdose; pharmacokinetics

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## Learning objectives

After reading this article, you should be able to:

- understand the mechanisms of drug metabolism by the liver
- have an appreciation of alterations to drug choice and dosing regimens in patients with liver disease due to their altered pharmacokinetics
- know the management of a patient with paracetamol overdose

## Liver anatomy

The liver receives approximately 30% of cardiac output. Uniquely it receives both arterial blood from the hepatic artery and venous blood from the portal veins. The portal vein supplies 70–75% of hepatic blood flow but only 50% of oxygen supply, the remaining blood flow and oxygen supply being from the hepatic artery.

Anatomically the liver is divided into two lobes and further into functional lobules based around a central vein, which contains blood from the hepatic arterial and portal venous circulations. Blood arriving to the liver flows into the sinusoids, which are spaces lined by hepactocytes. Blood then drains towards the centre of the lobule and the central vein, then hepatic vein to return blood back to the heart via the inferior vena cava. It is the portal veins taking blood directly from the gut to the liver that allows for first pass metabolism, making the liver susceptible to ingested drugs as they are absorbed from the gastrointestinal tract and transported to the liver.

The liver has a broad range of functions categorized in Table 1.

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## Metabolism of drugs by the liver

The liver metabolizes a wide range of drugs, the end result being to produce water soluble compounds which can be excreted in the bile. This results from phase 1 reactions mediated by cytochrome P450 including oxidation, reduction and hydrolysis reactions. This is followed by phase 2 reactions which are conjugative.

### Cytochrome P450

The cytochrome P450 family are a group of enzymes found mainly in the liver, which perform oxidation and reduction reactions (phase 1) using iron to enhance the water solubility of drugs to aid excretion. CYP450 enzymes are so named as they are bound to membranes within the cell and contain a haem pigment that absorbs light at a wavelength of 450 nm when exposed to carbon monoxide.

There are many different isoforms of CYP450, classified according to their amino acid sequencing into families, subfamilies and individual genes. Their importance can be seen in certain subgroups that lack particular genes. An example pertinent to anaesthesia is deficiency in CYP2D6 which metabolizes codeine to morphine; these patients therefore find codeine ineffective. Conversely there is a small subgroup of people of Saudi Arabian and Ethiopian decent with very high expression of 2D6 who metabolize codeine into vast amounts of morphine (refer to Table 2 for more details). An individual more detailed breakdown of CYP450 genes is beyond the scope of this article.

Some drugs can induce or inhibit CYP450 enzymes which have the sequential effect on the metabolism of other drugs, either increasing or reducing it, respectively. Possibly the most important example is CYP3A4 which metabolizes many substrates and is induced by rifampicin, carbamazepine, phenytonin and dexamethasone. Of interest to anaesthesia, this will increase metabolism of opioids, benzodiazepines and local anaesthetics. Another well-cited example is the increased metabolism of the oral contraceptive pill and its reduction in efficacy. For a more exhaustive list of substrates, inducers and inhibitors see Table 3.

A number of non-cytochrome P450 dependent reactions occur in the liver, for example oxidation of dopamine and alcohol, and hydrolysis of amides and esters (e.g. lignocaine and pethidine, respectively).

## Patterns of LFT derangement

A predominant rise in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) signals hepatocellular injury or death. This can be caused by drug reactions or toxicity (e.g. paracetamol), viral hepatitis, autoimmune hepatitis, alcoholic

## Functions of the liver

| Categories | Subcategories |
|---|---|
| Metabolic | Carbohydrates: gluconeogenesis, storage & breakdown of glycogen |
| | Proteins: including deamination of ammonia to form urea |
| | Fats: triglycerides & cholesterol |
| | Bilirubin; conjugation to become water soluble |
| | Drugs: transforming from lipid to water soluble by oxidation, conjugation, reduction, hydrolysis, methylation & acetylation |
| Synthetic | Haematological role: production of clotting factors (II, V, VII, IX, X and XI), protein C, protein S and anti-thrombin |
| | Bile acids |
| | Plasma cholinesterases |
| | Albumin and α1-acid glycoprotein |
| Storage | Vitamin storage: A,D, K, B12 and folate |
| | Glycogen |
| | Iron and copper |

**Table 1**

hepatitis, ischaemic hepatitis secondary to profound hypotension, and rare causes such as Wilson's disease.

An obstructive pattern has a rise predominantly in alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT), these are canalicular enzymes and suggest cholestasis. This is caused by obstruction, either calculi or tumour (primary bilary, pancreatic or metastases), and liver disease such as primary bilary cirrhosis. Pharmacological causes include antibiotics, anabolic steroids and oral contraceptives.

A mixed pattern can be seen in sepsis, some drug reactions, cholangitis, congestive cardiac failure and alcoholic liver disease. Halothane hepatitis can cause raised liver enzyme assays, raised bilirubin and jaundice. An isolated rise in unconjugated bilirubin may be attributed to Gilbert's syndrome or haemolysis.

## Pharmacokinetic effects of liver disease

### Absorption

Most drugs given in anaesthesia and intensive care are given intravenously, thus having a bioavailability of 1. However, some may be given orally or nasogastrically and absorbed enterally. The absorption will be affected by delayed gastric emptying or reduced by diarrhoea and increased gastric transit time seen in liver failure. Additionally if vasopressors are used there may be splanchnic vasoconstriction with associated reduced absorption.

## Prevalence of ultra-rapid metabolizers[8]

| Population | Prevalence of ultra-rapid metabolizers |
|---|---|
| African or Ethiopian | 29% |
| African American | 3.4–6.5% |
| Asian | 1.2–2% |
| Caucasian | 3.5–6.5% |
| Greek | 6% |
| Hungarian | 1.9% |
| Northern European | 1–2% |

**Table 2**

### Volume of distribution

Volume of distribution is a theoretical calculated volume within which a dose of a drug is dissolved. Hepatic dysfunction can cause fluid retention and will increase the volume within which drugs are present, particularly those which usually remain in the plasma, thus increasing their volume of distribution and reducing their plasma concentration.[1]

In liver disease, protein synthesis may be reduced. These proteins are important as binding sites for drugs and as such alter the amount of free drug available, volume of distribution, half life and duration of action. An important example is albumin. Hypoalbuminaemia will increase the proportion of free drug which is active, therefore doses of highly protein-bound drugs may need to be reduced, for example phenytonin and benzodiazepines, aspirin and warfarin.[2]

Another protein produced by the liver, $\alpha_1$ acid glycoprotein binds basic drugs such as carbamazepine, propanolol, alprenolol and imipramine as well as steroids. Bilirubin can also compete for protein binding sites, so raised levels can increase amount of free drugs, the effect however is less in vivo than in vitro.[3]

### Metabolism and elimination

Problems with absorption of enterally delivered drugs have been described. Once absorbed these drugs undergo the 'first pass effect' by the liver before reaching the systemic circulation. In liver failure the degree of metabolism will be reduced, therefore the extraction ratio will also be reduced and more drug will reach the systemic circulation, thus increasing bioavailability.

Metabolism of drugs in liver disease depends on liver blood flow. This can be reduced in a cirrhotic liver as portovenous shunting in the form of varices which are created and blood is diverted directly into the systemic circulation by-passing the liver. Thus first pass metabolism is reduced.

Drug metabolism by the liver may also be reduced by the use of vasopressors on intensive care, which reduce liver blood flow due to varying degrees of splanchnic vasoconstriction. The phase 1 and 2 reactions performed by the liver are affected and metabolism and thus extraction ratios are reduced.

Drugs can be divided into those with high extraction ratios $>0.7$, for example fentanyl and morphine and low extraction ratios $<0.3$ such as lorazepam, diazepam and methadone. Most drugs have low extraction ratios $<0.3$, that is they have poor permeability and are metabolized by the liver but poorly extracted, therefore clearance is limited by reduced metabolism not by blood flow. Those with high extraction ratios $>0.7$ are highly permeable and clearance is dependent on blood flow.[3]

## Drug dosage in liver disease

Hepatic dysfunction is not uncommon within the intensive care setting affecting 11–54% of critically ill patients depending on definitions used.[1] There is currently no tool akin to renal clearance to indicate degree of liver dysfunction.[3] Therefore clinicians