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

Royal College of Anaesthetists CPD Matrix: 1A02

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.

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

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

Functions of the liver

Categories	Subcategories
Metabolic	Carbohydrates: gluconeogenesis, storage and 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 and 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

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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

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 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

Cytochrome P450 substrates, inhibitors and inducers

Function	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP2E1	CYP3A4
Substrates of isoenzyme	Clozapine Imipramine Propanolol Theophyline Warfarin	Amitriptyline Diazepam Imipramine Lansoprazole Omeprazole Phenytonin	Amitriptyline NSAIDS[a] Losartan Phenytonin Warfarin	Amitriptyline Codeine Metoprolol Oxycodone Paroxetine Tramadol	Paracetamol Ethanol Halothane Isoflurane Isoniazid	Calcium channel blockers Carbamazepine Erythromycin Fentanyl Midazolam Simvastatin
Inhibitors of isoenzyme	Cimetidine Ciprofloxacin Citalopram Diltiazem Erythromycin	Cimetidine SSRIs[b] Lansoprazole Omeprazole	Amiodarone Fluconazole SSRIs[b] Metronidazole Trimethoprim	Amiodarone Chlorpheniramine SSRIs[b] Haloperidol Sertraline	Disulfiram	Amiodarone Cimetidine Grapefruit juice Omeprazole Verapamil
Inducers of isoenzymes	Carbamazepine Tobacco	Carbamazepine norethindrone	Phenobarbitone Rifampicin		Chronic ethanol Isoniazid Tobacco	Carbamazepine Rifampicin Rifabutin

[a] Non-steroidal anti-inflammatory drugs.
[b] Selective serotonin reuptake inhibitors.

Table 3

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