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# 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,<sup>1</sup> Correct and early management is crucial and will be discussed within this article.

**Keywords** Paracetamol overdose; cytochrome p450; hepatic failure; liver; metabolism; pharmacokinetics

## 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 hepatocytes. 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 which 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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## Learning objectives

After reading this article you should:

- 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

## Metabolism of drugs by the liver

The liver metabolises 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.

## Functions of the liver

Categories	Subcategories
Metabolic	Carbohydrates; gluconeogenesis, storage and breakdown of glycogen Proteins; including deamination of ammonia to form urea Fats; triglycerides and 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 $\alpha$ 1-acid glycoprotein
Storage	Vitamin storage; A, D, K, B12 and folate Glycogen Iron and copper

Table 1

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 metabolises codeine to morphine, these patients therefore find codeine ineffective. Conversely there is a small subgroup of people of Saudi Arabian and Ethiopian descent with very high expression of 2D6 who metabolize codeine into vast amounts of morphine. See 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 metabolises many substrates and is induced by rifampicin, carbamazepine, phenytoin 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, e.g. 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 biliary, pancreatic or metastases), and liver disease such as primary biliary 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.

### Prevalence of ultrarapid metabolisers<sup>2</sup>

Population	Prevalence of ultrarapid metabolisers
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

### Pattern of LFT derangements with COVID-19 infection

The SARS-CoV-2 virus uses angiotensin-converting enzyme 2 (ACE-2) receptors to gain entry into cells.<sup>3</sup> Liver particularly in the ductal region has abundance of these receptors, and hence may be susceptible to SARS-CoV-2.<sup>4</sup> Elevated LFT have been reported widely in hospitalized patients with COVID-19; the range of elevation is highly variable, from 14 to 58%.<sup>4–7</sup> Surprisingly, the pattern of elevation mimics hepatocyte damage (AST/ALT higher than bilirubin or ALP) rather than cholangiocytic damage, as would have been expected given that the density of ACE-2 receptors is higher in the ductal system.<sup>4</sup> Additionally low albumin has been seen and is a marker of severe disease.<sup>5</sup> One study reported longer hospital stay in patients with elevated LFT.<sup>6</sup>

An international registry has suggested that as many as 25% of patients with COVID-19 may present with hepatic decompensation in the absence of respiratory symptoms.<sup>7</sup>

The above findings hold important implications for anaesthetists, especially in preoperative assessments.

### 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.

#### 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.<sup>8</sup>

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. Hypo-albuminaemia will increase the proportion of free drug which is active; therefore doses of highly protein bound drugs may need to be reduced, for example phenytoin and benzodiazepines, aspirin and warfarin.<sup>8</sup>

Another protein produced by the liver,  $\alpha_1$  acid glycoprotein, binds basic drugs such as carbamazepine, propranolol, alprenolol and imipramine as well as steroids. Bilirubin can also compete for protein binding sites, so raised levels can increase the amount of free drugs; the effect however is less in vivo than in vitro.<sup>9</sup>

#### 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.

### Cytochrome P450 substrates, inhibitors and inducers

Function	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP2E1	CYP3A4
Substrates of isoenzyme		amitriptyline	amitriptyline	amitriptyline	paracetamol	calcium channel blockers
	clozapine		NSAIDs <sup>a</sup>	codeine		carbamazepine
	imipramine	diazepam			ethanol	erythromycin
		imipramine		metoprolol	halothane	
	propranolol	lansoprazole	losartan	oxycodone	isoflurane	fentanyl
	theophylline	omeprazole		paroxetine	isoniazid	midazolam
	warfarin	phenytoin	phenytoin	tramadol		
Inhibitors of isoenzyme			warfarin			simvastatin
	cimetidine	cimetidine	amiodarone	amiodarone	disulfiram	amiodarone
	ciprofloxacin	SSRIs <sup>b</sup>	fluconazole	chlorpheniramine		cimetidine
	citalopram	lansoprazole	SSRIs <sup>b</sup>	SSRIs <sup>b</sup>		grapefruit juice
	diltiazem	omeprazole	metronidazole	haloperidol		omeprazole
	erythromycin					verapamil
			trimethoprim	sertraline		
Inducers of isoenzymes	carbamazepine	carbamazepine	phenobarbitone		chronic ethanol	carbamazepine
	tobacco	norethindrone	rifampicin		isoniazid	rifampicin
					tobacco	rifabutin

<sup>a</sup> Non-steroidal anti-inflammatory drugs.

<sup>b</sup> Selective serotonin reuptake inhibitors.

**Table 3**

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 bypassing 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.<sup>9</sup>

#### 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.<sup>9</sup> There is currently no tool akin to renal clearance to indicate degree of liver dysfunction.<sup>13</sup> Therefore clinicians use liver function blood tests, international normalized ratio (INR), serum albumin and clinical scores such as the Child Pugh score act as a surrogate for function. More recently the Model for End Stage Liver Disease (MELD Score) and the MELD-Na have been used to more accurately predict the severity of liver dysfunction.<sup>10,11</sup> However, their correlation with pharmacokinetic function not well understood.

### Summary of recommendations for opioid use in patients with liver disease

Name of drug	Half life in normal patients	Half life in patient with liver disease	Recommended dosing	Special consideration
Tramadol	5–6hrs	13–14hrs	50mg BD	Avoid in epileptic patients Risk of serotonin syndrome and/or toxicity with SSRI /TCA co administration
Oxycodone	4–5 hrs	14hrs	5mg max QDS	Variable onset and efficacy
Morphine	3–4hrs	5hrs	5mg max QDS	Avoid with coexisting renal failure Prefer to Use elixir form
Methadone	19hrs	35Days	Not recommended, except as part of deaddiction programme	Seek expert help in dosing

**Table 4**

Due to the alterations discussed in pharmacokinetics in liver dysfunction drug choices, dosages and frequency may need to be rationalized and altered accordingly. For example the induction dose and maintenance dose, for either anaesthesia or sedation, needs to be reduced.

### Inhalational agents

Historically inhalational agents, particularly halothane have been implicated in causing hepatitis. The risk is related to the generation of trifluoroacetyl chloride (TFA) by metabolism of agents, which is implicated in toxicity.<sup>12</sup> Around 20% of administered dose of halothane is metabolized by the liver, more specifically by cytochrome P450. This is a relatively high percentage when compared to more modern inhalational agents, for example 0.2% isoflurane, 0.02% desflurane and 3% sevoflurane. Even though sevoflurane undergoes 3% metabolism it does not generate TFA and hence is not linked to immune mediated injury.<sup>13</sup> Sevoflurane metabolism produces fluoride which is not linked to hepatotoxicity.<sup>14</sup> Inhalational agents themselves cause a dose dependent reduction in hepatic blood flow (HBF). Isoflurane and sevoflurane result in relatively lower reduction in HBF at 1 MAC as compared to desflurane.<sup>15</sup>

As long as hypotension is avoided and the above effects are kept in mind desflurane is probably the safest choice of inhalational agent due to its low rate of metabolism and rapid and predictable emergence from anaesthesia.<sup>13</sup>

There are two types of halothane hepatitis. Type 1 which is mild, transient and has a relatively high incidence (25–30%). Type 2 caused by oxidative metabolism of halothane in the liver leading to fever, jaundice, and dramatically elevated serum transaminases. The compounds synthesized by oxidation then bind to trifluoroacetyl proteins in the hepatic endoplasmic reticulum causing cellular dysfunction; it is thought to occur in genetically predisposed individuals.

The Committee on Safety of Medicines in 1986 recommended the avoidance of halothane in patients with a history of previous adverse reactions, those who had received halothane within 3 months unless clinically necessary, and those with a history of unexplained jaundice or pyrexia following previous halothane anaesthesia.

**IV Anaesthetics:** the induction agents have a marked effect on haemodynamics and may cause sudden precipitous fall in blood pressure. In clinical practice a standard induction dose need not be altered. However, they should be titrated slowly to effect. There are no current recommendations on the use of TIVA (Total Intravenous Anaesthesia) in patients with liver disease. Research is sparse and conflicting. Some earlier reports suggested that inhalational anaesthesia results in smaller elevation of liver enzymes than TIVA with propofol-fentanyl.<sup>16</sup> A more recent study however, suggested a slightly lower rate of elevation in LFT after using TIVA.<sup>17</sup>

### Opiates

Morphine is metabolized by the liver to active metabolite morphine-6-glucuronide which has potent analgesic properties, and morphine-3-glucuronide, which has no analgesic properties but has adverse neurotoxic side effects such as confusion and respiratory depression. As both metabolites are excreted renally, they accumulate in renal failure. In liver failure morphine itself may accumulate as extraction ratio is reduced thereby enhancing

further the effect of morphine.<sup>13</sup> Therefore, the dose of morphine should be reduced. The same is true of fentanyl and alfentanil dose, as although there is no active metabolite they also rely on hepatic metabolism. Remifentanyl may be a good choice as its metabolism is by plasma esterases and it has no active metabolites. A review of pain management in patients with liver disease by the American Association for Study of Liver Diseases (AALSD) in 2018 states in general most opioids have prolonged half life. Their recommendations include increasing the dosing intervals (6–12 hours) and using immediate release preparations over extended release (Table 4).<sup>18</sup>

In July 2013 the Medicine and Healthcare products Regulatory Agency (MHRA) produced a drug safety update that restricted the use of codeine in children.<sup>19</sup> This was prompted by case reports of four children who suffered serious harm following the administration of codeine in the immediate postoperative period. Codeine should only be used to relieve acute moderate pain in children older than 12 years and only if it cannot be relieved by other painkillers such as paracetamol or ibuprofen alone.

A significant risk of serious and life-threatening adverse reactions has been identified in children with obstructive sleep apnoea who received codeine after tonsillectomy or adenoidectomy (or both). Codeine is now contraindicated in all children younger than 18 years who undergo these procedures for obstructive sleep apnoea.

Codeine is converted to morphine in the liver by the CYP2D6 enzyme. The extent of conversion of codeine to morphine depends on genetic variations of CYP2D6. People can be classified as: poor; intermediate; extensive; or ultra-rapid metabolisers. Poor metabolisers convert very little codeine into morphine and therefore have little or no pain relief; ultra-rapid metabolisers or extensive metabolisers have an excessive amount of morphine in their blood following ingestion of codeine. Ethnic origin is an important factor in genetic variability. Up to 10% of Caucasians are poor metabolisers whereas up to 29% of patients of African origin may be ultra-rapid metabolisers (see Table 2).

This genetic variability leads to different plasma morphine concentrations in patients leading to different analgesic effects as well as side effects including respiratory depression.

Codeine is contraindicated in all patients of any age known to be CYP2D6 ultra-rapid metabolisers and should not be used by breastfeeding mothers because it can pass to the baby through breast milk and potentially cause harm.

### Other analgesics

NSAIDs are contraindicated for systemic use in most liver disease patients, because of increased bioavailability, the high risk of precipitating gastrointestinal bleeding and renal failure.<sup>20</sup> Pregabalin and gabapentin are not metabolized in the liver and can be considered for use. These drugs are renally excreted, therefore patients with hepatorenal syndrome warrant cautious administration.<sup>18,20</sup> Gabapentin is considered as first line non-opioid drug for analgesia. Among the tricyclic antidepressants nortriptyline appears safer than amitriptyline and imipramine.<sup>20</sup>

### Neuromuscular blockers

An increased dose of non-depolarising neuromuscular blockers (NMB) may be required in liver disease possibly due to altered

protein binding and increased volume of distribution. However, those which are metabolized by the liver have a prolonged duration of action, atracurium as metabolized in the plasma has a more predictable duration of action. However, it is worth noting that in prolonged usage concentrations laudanosine from Hoffmann degradation may accumulate with the potential to provoke epileptiform activity on electroencephalography (EEG).<sup>13</sup> This is of greater concern if the patient has concomitant renal failure or impaired blood brain barrier. The metabolism of succinylcholine may be prolonged due to reductions in pseudocholinesterase concentrations, but clinically this is of little significance.

### Suggamadex

Suggamadex is a unique reversal agent for amniosteriodal NMB which acts by chelating the NMB. It is not metabolized and is excreted almost exclusively unchanged by the kidneys within 24 hours.

Data regarding use of sugammadex, in patients with liver dysfunction is limited. However, as sugammadex is almost entirely excreted renally, no dose reduction is required in patients with mild to moderate liver dysfunction. In patients undergoing liver transplant, sugammadex is able to reverse neuromuscular block maintained by rocuronium continuous infusion.<sup>21</sup> However, it is important to note that the sugammadex recovery time in this population was found to be considerably longer than in other surgical settings, and should be considered in clinical practice.

### Dexmedetomidine

Dexmedetomidine is a highly selective alpha-2 receptor agonist, with analgesic, anxiolytic and sedative properties. It is primarily metabolized in the liver and may have a prolonged half-life in patients with

liver disease. Dexmedetomidine has potential protective effects on the liver and intestine during hepatectomy and intra-operative use during liver surgery is subject to ongoing research.<sup>22</sup>

Additionally, patients with elevated bilirubin and bile salts secondary to jaundice may show bradycardias limiting its use.<sup>23</sup>

### Paracetamol overdose

Paracetamol is the most common drug taken in overdose in the UK to date; it can result in liver failure and in some cases is fatal.<sup>1,24</sup> Hepatocellular necrosis can occur if as little as 7.5 g of paracetamol is ingested. Normal pathways of metabolism are saturated and hepatic glutathione stores are exhausted. Patients are often initially asymptomatic for the first 24 hours before reporting nausea, vomiting, right upper quadrant pain with progressive derangement of liver function tests (LFTs) after 18 hours. The MHRA produced new guidelines for treatment of paracetamol overdose in 2012; the changes included an updated nomogram and a simplified treatment schedule.<sup>25</sup>

The administration of acetylcysteine has previously been based on the Rumack-Matthew nomogram, which divided treatment groups into high and low risk. The dose was then calculated on a weight-based table, which increased the risk of drug error. The updated nomogram has a single treatment line (Figure 1);<sup>25</sup> thereby eliminating the need for assessing whether the patient falls into the high-risk category. It also advises that in cases of staggered overdoses there should be no delay in the administration of acetylcysteine. Another cause for concern was the adverse events that had been reported following the bolus dose of acetylcysteine; this has been addressed by increasing the duration over which it is infused, from 15 to 60 minutes.

Acetylcysteine should be administered when the plasma paracetamol level is on or above a single treatment line

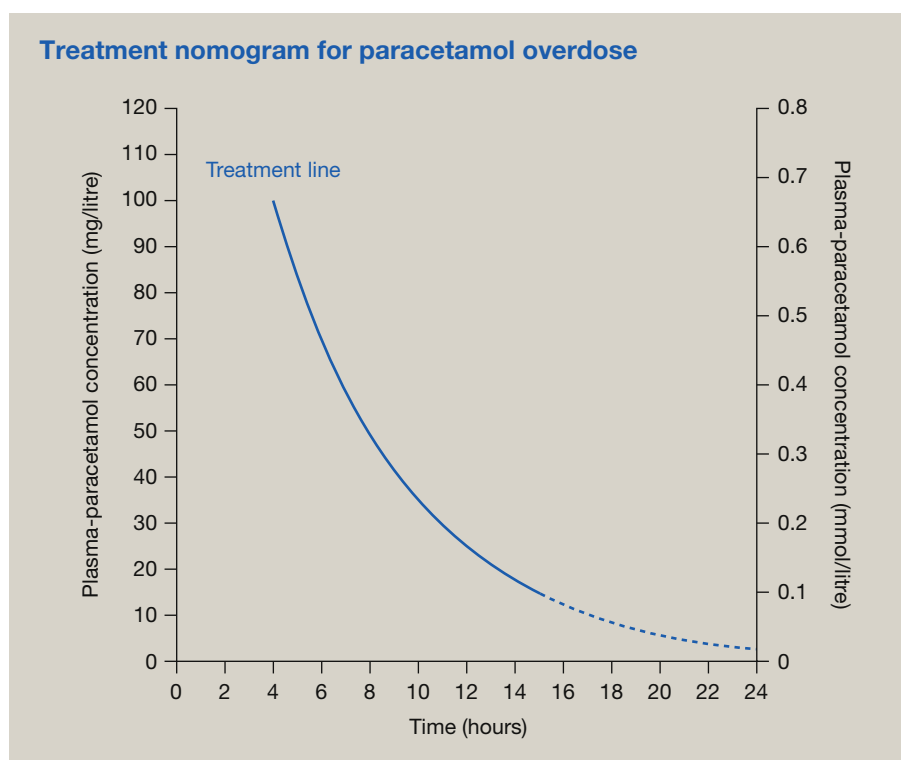


Figure 1 Treatment nomogram for paracetamol overdose.

joining points of 100 mg/L at 4 hours and 15mg/L at 15 hours after ingestion. A baseline full blood count (FBC), urea and electrolytes (U&Es), LFTs and coagulation screen along with an arterial blood gas sample should also be done at the earliest opportunity.

Intravenous preparations of paracetamol were licensed in the UK in 2004 and it is routinely used in anaesthetic practice. However, there have been some concerns regarding the dosage and administration, especially in adults and children under 50 kg, patients with pre-existing hepatic dysfunction and the elderly. Children and infants weighing less than 10 kg should receive the reduced dose of 7.5 mg/kg not exceeding the daily dose of 30 mg/kg, whilst those >10 kg can be prescribed up to 15 mg/kg not exceeding the daily dose of 60 mg/kg.

Both the MHRA and the NPSA have issued alerts, regarding the correct dose prescription as there have been reported cases of accidental overdose due to millilitre to milligram conversion and the administration of 1 g in adults weighing less than 50 kg. The key issue is that with intravenous paracetamol, plasma levels will peak immediately after administration. The traditional nomograms used to predict plasma levels after overdose refer to oral ingestion where the levels peak some hours afterwards.

Indicators of severe paracetamol poisoning which is likely to require referral to a specialist liver centre include: INR of >2.0 at 24 hours, >4 at 48 hours or >6 at 72 hours; renal impairment (creatinine >200 micromol/l); hypoglycaemia; metabolic acidosis despite rehydration; hypotension despite resuscitation or encephalopathy.<sup>26</sup>

The only other treatment in fulminant liver failure is transplantation.

#### Paracetamol as analgesic in chronic liver disease

Given the potential of paracetamol to cause liver injury, there is a common misconception that these patients should *never* take paracetamol. However, various studies have shown that if taken in appropriate doses, paracetamol is one of the safest analgesics for patients with cirrhosis. Limiting the total daily dosage to 2–3 g/day with thrice daily dosing is generally recommended.<sup>27</sup> Patients should be educated about over-the-counter and prescription medications that may also contain acetaminophen to avoid overdose.

#### COVID-19 specific therapy and the liver

**Remdesivir:** elevated liver enzymes are commonly observed in clinical trials of patients with remdesivir.<sup>28</sup> The elevated values rarely warrant treatment discontinuation. Current recommendations suggest that if the enzymes are elevated to five times or more above baseline, the drug should be discontinued.

**Tocilizumab:** ALT elevations are frequent but fulminant hepatitis is rare. The risk of reactivation of HBV should be kept in mind if the patient had chronic liver disease secondary to viral aetiology.<sup>28</sup>

**Steroids:** low dose dexamethasone is probably safe in patients with chronic stable liver disease. However, use of methylprednisolone in high doses may reactivate HBV and increase the risk of spontaneous bacterial peritonitis (SBP) in severe cases.<sup>28</sup>

**Hydroxychloroquine:** data is limited but generally has not been associated with elevations in ALT levels and is an extremely rare cause of drug induced liver injury.<sup>28–30</sup> ◆

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