Drugs and the liver

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Abstract

The liver is crucial in drug handling, but can also be injured by drugs. Intensivists and anaesthetists will frequently encounter patients with acute, chronic, and acute-on-chronic liver dysfunction, each of which pose distinct management challenges. Moreover, even in the healthy liver, inter-individual variability in liver enzyme metabolic function may markedly impact intended and unintended drug effects. This updated review provides an overview of hepatology concepts that are most relevant to intensivists and anaesthetists, with a focus on medicines. The relationship between medicines and liver function and physiology are discussed, with reference to clinical contexts seen in the critically ill patient. We also describe an approach to the diagnosis and management of drug-induced liver injury in the intensive care unit, and recent changes to recommended practice in management of paracetamol (acetaminophen) toxicity.

Keywords Drug metabolism; hepatology; liver; liver failure; medications; pharmacology

Royal College of Anaesthetists CPD Skills Framework: Pharmacology and therapeutics

Learning objectives

After reading this article, you should be able to:

- describe drug disposition and metabolism by the liver with reference to medicines and clinical scenarios commonly encountered by intensivists and anaesthetists
- apply a structured approach to drug-induced liver injury, with a focus on classic offenders in intensive care and perioperative settings
- recognize when and how states of altered liver physiology and acute failure can affect critical care and anaesthetic medicines
- update clinical practice knowledge on the management of paracetamol (acetaminophen) toxicity

Introduction

The liver is an essential visceral organ with various metabolic, synthetic, and storage roles.[1] It plays an important role in the processing of substances, such as drugs, absorbed from the gut lumen before they enter the systemic circulation. While many drugs are administered intravenously in critical care, changes in liver function — either chronic or in the context of critical illness or acute liver failure — can substantially alter the pharmacokinetics and pharmacodynamics of many intravenous medicines too. Moreover, the liver can be the victim of adverse drug reactions, resulting in injury, and sometimes being the underlying cause of liver failure. Acute liver failure (ALF) is defined as a combination of coagulopathy (international normalized ratio $\geq$1.5), acute liver injury (<26 weeks with no known pre-existing liver disease), and hepatic encephalopathy. Acute-on-chronic liver failure (ACLF) occurs in individuals with established chronic liver disease, and is characterized by acute decompensation accompanied by extrahepatic organ dysfunction or failure. Both ALF and ACLF are associated with poor transplant-free survival (22–74% depending on aetiology and severity) and, unlike for renal failure, there are currently no extracorporeal liver replacement therapies in widespread clinical use.

For these reasons, an understanding of pharmacological principles is crucial when managing patients with liver injury or dysfunction. This can improve drug selection and dosing decisions, help to anticipate when a disease state may alter drug response or toxicity, and recognize when a drug may be implicated in liver injury or failure.

In this review article, we first outline hepatic pharmacology fundamentals and discuss how these can be applied in practice when prescribing in critical care scenarios. Next, we describe a suggested approach to investigating and managing a suspected drug-induced liver injury in the intensive care unit. Finally, we review management principles in paracetamol (acetaminophen) overdose, including a summary of recent changes to recommended clinical practice for N-acetylcysteine (NAC) infusions.

The liver and drug handling

In healthy individuals the portal vein transports virtually all venous blood originating from the gut to the liver. This provides up to three quarters of hepatic blood supply — with the remainder derived from the hepatic artery — and exposes many absorbed substances to varying degrees of hepatic metabolism before they enter the systemic circulation. For drugs administered enterally, this initial processing before onward passage to the systemic circulation is termed first pass metabolism. Drugs administered intravenously completely bypass hepatic first pass effects, however, the liver remains an important site of metabolism and elimination for many of them.

Metabolism of drugs is often divided into phase I (functionalization) and phase II (conjugation) reactions; both occur predominantly in the liver. In reality, phase I and II pathways overlap and do not necessarily occur sequentially, but the framework remains helpful for understanding drug–drug interactions, toxicity, and inter-individual variability in what can often be complex, multi-step metabolic pathways.[2]

Phase I and first pass metabolism

Most first pass metabolism and many other phase I reactions are mediated by cytochrome P450 monooxygenase (CYP) enzymes,

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which are expressed in many tissues but highly concentrated in the liver. Phase I reactions include oxidation, reduction, and hydrolysis, and typically add or expose functional groups to increase substrate polarity. This increased polarity yields a more water-soluble metabolite that can be more easily conjugated in phase II, or directly excreted in the urine or bile.[2] In most instances, phase I metabolism serves to inactivate a given drug, but in certain cases may produce a more potent metabolite (e.g. clobazam → N-desmethylclobazam, mediated by CYP2C19), a toxic metabolite (e.g. paracetamol → N-acetyl-p-benzoquinone imine [NAPQI], mediated by CYP2E1), or activate an inactive drug (e.g. codeine → morphine, mediated by CYP2D6).

The CYP system is of particular clinical importance because a small portion of CYP enzymes are collectively responsible for the metabolism of the majority of marketed drugs.[3] Moreover, their activity is influenced by both genetic variation and environmental factors, resulting in inter-individual variability in drug efficacy and safety.

Drugs are themselves environmental exposures that can alter CYP activity through induction and inhibition. The list of potential CYP enzyme modulators is large, and detailed tables of specific drug–enzyme interactions can be found elsewhere.[1] Here we illustrate a general principle with one critical care-relevant example. In addition to classic enzyme inducers (e.g. carmabazepine, phenytoin, rifampicin), corticosteroids such as dexamethasone are capable of enzyme induction, particularly of CYP3A4 and CYP2C9.[4] The effect of this is to reduce exposure to, and potential efficacy of, co-administered CYP3A4 and CYP2C9 substrates. These include various benzodiazepines, antimicrobials, opioids and immunosuppressants among others. The inverse – i.e. increased exposure and risk of toxicity – can be effected by CYP enzyme inhibition.

Even in the absence of pre-existing liver disease, systemic inflammation can downregulate drug-metabolising enzyme expression and activity.[5] Clinically, this means that CYP-metabolized drugs may accumulate or demonstrate prolonged effects in sepsis or critical illness, even with normal or only mildly deranged biochemical markers of liver function.

Phase II metabolism

Phase II reactions generally increase polarity via conjugation (e.g. glucuronidation, sulfation, glutathione conjugation). As with phase I metabolism, this can facilitate biliary or renal elimination.

Glucuronidation is highly relevant to anaesthesia because propofol is predominantly cleared via this process, by an isoform of the enzyme uridine 5′-diphospho-glucuronosyltransferase (UGT). Various other critical care medicines rely on glucuronidation at some stage of their metabolism, for example, dexmedetomidine also undergoes extensive hepatic glucuronidation and hydroxylation as part of its metabolism and elimination pathway. While thought to impact drug exposure to a lesser extent, and hence less studied than CYP-mediated drug interactions, UGT induction and inhibition is an important mechanism of potential drug–drug interaction.[6]

Glutathione is a key antioxidant and detoxification molecule. Conjugation to glutathione is an important phase II reaction, neutralizing reactive electrophiles and limiting harmful covalent binding to cellular proteins.[7] It warrants special mention in this review because of its essential role in preventing paracetamol toxicity;[8] further information on the management of paracetamol overdose is provided later in this article. However, glutathione conjugation is involved in the detoxification of multiple other medicines – particularly their reactive metabolites – including phenytoin, carbamazepine, phenobarbital, and sevoflurane.

Clinical relevance of hepatic extraction ratio

Hepatic extraction ratio describes the fraction of drug removed from circulation by the liver during a single pass. In the classic 'well-stirred' model, hepatic clearance is determined by hepatic blood flow, intrinsic metabolic capacity and the unbound fraction of circulating drug.[8] High extraction drugs (e.g. propofol, fentanyl, lidocaine, morphine) are usually flow-limited, meaning hepatic clearance depends heavily on blood flow, with enzyme activity and protein binding being less influential. Conversely, low extraction drugs (e.g. diazepam, phenobarbital, amiodarone, theophylline) are often more capacity-limited, meaning clearance depends more on metabolic enzyme activity and drug–protein binding than hepatic blood flow. These drugs can therefore be more sensitive to hypoalbuminaemia and altered enzyme activity in the context of drug–drug interaction or systemic inflammation. The impact of protein binding is complex, however, and clinical implications are likely limited in most cases.[9]

Pharmacogenetics

Pharmacogenetics is the study of individual genetic variants that can impact drug disposition and response, for example those affecting transporters, receptors, or metabolic enzymes. Many of these variants occur in genes that encode proteins which are in turn highly expressed in the liver. CYP enzymes are a particularly pertinent example both because of their involvement in the metabolism of a large proportion of clinically used drugs, and considerable inter-individual genetic variability that can alter enzyme function. However, genes and proteins that are of clinical relevance span diverse families and patterns of tissue expression.

Pharmacogenetic testing has been adopted widely for several clinically important drug–gene interactions, including HLA-B*57:01 screening prior to abacavir therapy, TPMT and NUDT15 testing before thiopurine treatment, and DPYD testing for fluoropyrimidines. In contrast, pharmacogenetic testing for CYP genes and critical care-relevant drugs remains more variable between healthcare systems and settings, although broader adoption is anticipated as evidence accumulates and testing becomes more accessible. Emerging examples include CYP2C19-guided antiplatelet therapy and point-of-care MT-RNR1 genotyping to prevent aminoglycoside-associated ototoxicity. Notably, the latter has already implemented in some neonatal intensive care centres.[10] Moreover, with large-scale prospective programmes evaluating pre-emptive, panel-based genotyping underway,[11] it is conceivable that wider-ranging genetically informed drug decisions could become more commonplace over the coming years. Regardless of the availability of testing, an awareness of pharmacogenetic influences is important when recognizing and managing an exaggerated or resistant response to a drug.

Pharmacology in critical illness and liver dysfunction

Prescribing decisions for patients with liver dysfunction or failure require a cautious and holistic approach with close monitoring of

clinical and laboratory parameters. Important considerations include liver perfusion, hepatocellular injury (indicated by serum transaminase levels), synthetic function (indicated by INR and albumin), co-morbidities, and overall disease state. Manufacturers and regulators often use the Child–Pugh score (a clinical scoring system used to estimate the severity of liver disease in patients with cirrhosis) to stratify advice on use in hepatic impairment. However, this score is not validated in people with non-cirrhotic chronic liver disease.

Critical illness is also associated with a range of physiological alterations that may significantly impact hepatic drug handling. Table 1 summarizes these changes, with notes on their potential impact on a selection of drugs commonly used in critical care.

In many typical critical care scenarios, hepatic blood flow is reduced, for example: in shock, during extra-corporeal membrane oxygenation (ECMO), or with high positive end-expiratory pressure (PEEP). This decreased flow reduces hepatic clearance, particularly of drugs with a high hepatic extraction ratio, as the liver is unable to compensate for reduced flow with increased extraction. Toxicity can therefore occur more frequently, sometimes unexpectedly with low or moderate doses of these drugs.[12]

Both chronic liver disease and critical illness are also often associated with reduced serum albumin concentrations. For highly albumin-bound drugs, this can result in a much higher fraction of unbound drug circulating. This can be further compounded by increased serum bilirubin concentrations because bilirubin can compete with medicines for albumin binding sites. The effects of these changes are nuanced: higher free drug concentrations can augment peak effects while also exposing more drug for excretion. Therefore, in some cases the potential is for increased drug activity and risk of toxicity — even with apparently normal total plasma concentrations — and in others for reduced total exposure which can reduce efficacy for some medicines (e.g. aminoglycosides and vancomycin).

For drugs that are delivered orally or via enteral tube, portosystemic shunting in cirrhosis or acute portal hypertension can divert venous blood from the gut to collateral vessels, bypassing hepatocytes, reducing first pass metabolism and making bioavailability higher and more unpredictable.

Specific prescribing considerations

Coagulopathy and anticoagulation

Coagulopathy represents a special case because, while it is ubiquitous in ALF and very common in ACLF, INR is a poor predictor of bleeding risk in these contexts. Routine correction of coagulopathy is not recommended in the absence of bleeding or planned invasive procedures, and can interfere with prognostication or cause transfusion-related harm. Viscoelastic testing (e.g. thromboelastogram; TEG) may provide a better measure of haemostatic balance, but sparse evidence means this is not universally recommended.

Despite frequently having an abnormal INR/activated partial thromboplastin time (APTT), patients with ACLF are at high risk of venous thromboembolism (VTE). Prophylaxis with low-molecular-weight heparin, if there are no contraindications, is recommended in ACLF by the Society of Critical Care Medicine (SCCM).[13] No recommendation is made regarding pharmacological prophylaxis in ALF due to insufficient evidence, though

Physiological changes in intensive care/liver failure and how these can affect pharmacology

Physiological state	Functional impact	Pharmacokinetic consequence	Clinical consequence
Hepatic circulatory dysfunction			
Portosystemic shunting (cirrhosis, portal venous thrombosis)	First-pass metabolism bypassed	↑ oral bioavailability of drugs with high first-pass effects	Exaggerated effect from normal enteral doses. *Impacted drug examples*: diazepam, some opioids, many β-blockers and calcium-channel blockers
Reduced hepatic blood flow (shock, vasopressors; cirrhosis; ECMO, high PEEP)	↓ sinusoidal perfusion → flow-limited elimination falls	↓ clearance of high-extraction drugs	Accumulation, prolonged/exaggerated effect, delayed offset. *Impacted drug examples*: propofol, fentanyl/alfentanil, morphine, ketamine, lidocaine
Intrinsic liver dysfunction			
Inflammation-mediated enzyme suppression (sepsis, severe systemic inflammation)	Reduced CYP/UGT enzyme metabolic capacity	↓ intrinsic clearance (especially low-moderate extraction drugs)	Accumulation, prolonged/exaggerated effect, delayed offset. *Impacted drug examples*: midazolam (CYP3A4), fentanyl (CYP3A4), voriconazole (CYP2C19), lorazepam (UGT2B15), some anti-

			epileptics e.g. lamotrigine, valproic acid (various UGTs)
Hepatocellular dysfunction (ALF, ACLF, severe cirrhosis)	Loss of functional hepatocyte mass	Broad ↓ metabolic capacity (phase I + II)	Accumulation, prolonged/exaggerated effect, delayed offset. *Impacted drug examples:* Some benzodiazepines, propofol infusion, some opioids, many azoles, anti-arrhythmics and anti-epileptics
Altered drug distribution			
Hypoalbuminaemia (critical illness, acute and/or chronic liver failure)	↓ albumin available for drug binding	↑ free fraction for highly albumin-bound drugs	Strong effects or toxicity at therapeutic levels; total levels can be misleading, free drug levels are preferred.
NB the clinical implications of altered protein binding are limited in most circumstances		May be compounded by competitive displacement if ↑ bilirubin	*Impacted drug examples:* phenytoin, valproate, warfarin, ceftriaxone, midazolam
Ascites/third spacing (decompensated cirrhosis, hypoalbuminaemia)	↑ extracellular volume	↑ Vd for hydrophilic drugs; slower redistribution	Lower early concentrations, loading needs increased; delayed offset due to 'reservoir'. *Impacted drug examples:* hydrophilic antibiotics (e.g. β-lactams, aminoglycosides, vancomycin), some neuromuscular blockers, digoxin
Altered drug excretion			
Cholestasis (sepsis-associated, obstructive)	Impaired bile production and excretion, hyperbilirubinaemia	↓ biliary clearance of some drugs/metabolites	Accumulation, prolonged/exaggerated effect, delayed offset. *Impacted drug examples:* some neuromuscular blockers, ceftriaxone, some macrolides, rifampicin, some azole antifungals
Dynamic recovery phase (improving hepatic perfusion/function)	Flow and enzyme activity rebound	Clearance increases vs prior days	Falling levels, agitation/pain/seizure breakthrough. *Impacted drug examples:* sedatives/opiates (e.g. midazolam, fentanyl, propofol), anti-epileptics
Other			
Increased CNS sensitivity (hepatic encephalopathy, hyperammonaemia)	Neuroinflammation, increased BBB permeability	Pharmacokinetics may be unchanged, but effect-site sensitivity ↑	Stronger sedative/opioid effects, delirium, prolonged coma. *Impacted drug examples:* benzodiazepines, opioids, propofol, antipsychotics

BBB, blood–brain barrier; Vd, volume of distribution.

Table 1

the European Association for the Study of the Liver (EASL) suggests the need for VTE prophylaxis should be considered daily for these patients.[14]

Haemodynamic support and vasoactive agents

Crystalloid fluid resuscitation is recommended first-line for haemodynamic compromise, but excessive volume loading should be avoided due to the risk of cerebral oedema. SCCM suggests albumin over other fluids in ALF and ACLF, particularly when serum albumin is lower than 3 g/dl (30 g/litre).

If vasopressors are required due to low blood pressure, noradrenaline (norepinephrine) is the recommended first-line agent, with vasopressin added if required to reduce dose requirements (EASL guidance suggests either vasopressin or terlipressin). In ACLF complicated by hepatorenal syndrome, SCCM recommends vasopressors (noradrenaline, terlipressin, or midodrine and octreotide) over conservative management alone, with no specific recommendation to prioritize one vasopressor over another, while EASL suggest terlipressin should be first line in hepatorenal syndrome.

Antimicrobials

Patients with ALF and ACLF are at increased risk of infection; however, routine antimicrobial prophylaxis is not recommended in ALF, as they do not appear to reduce bloodstream infections or short-term mortality. In contrast, targeted prophylaxis is recommended in ACLF for specific scenarios, including upper gastrointestinal bleeding and spontaneous bacterial peritonitis. Antimicrobial selection and dosing should account for altered pharmacokinetics (though most do not require routine dose alteration), risk of further hepatotoxicity, and local resistance patterns and guidelines.

Drug-induced liver injury in intensive care

Drug-induced liver injury (DILI) is a heterogenous spectrum of liver damage caused by pharmaceutical agents, herbal and dietary supplements, and toxins, among others. Although uncommon, it is an important cause of ALF and presents unique diagnostic and management challenges in the critical care setting.[15] DILI is often categorized as either a) intrinsic; predictable, dose-dependent toxicity with a short latency (e.g. paracetamol), or b) idiosyncratic; unpredictable, dose-independent, with variable latency often of days to weeks after exposure. Both can present with hepatocellular, cholestatic, or mixed patterns of injury, and can mimic other causes of liver injury which complicates early recognition. While most cases of DILI have a favourable prognosis, those with idiosyncratic DILI progressing to ALF have very poor transplant-free survival (20–40% at 3 weeks).

The diagnosis of DILI – particularly idiosyncratic DILI – is frequently one of exclusion and it is important to consider other causes of acute liver injury such as critical illness cholestasis, shock and ischaemia, and liver injury mimics such as alkaline phosphatase (ALP) rise following bone fractures, or alanine aminotransferase (ALT) and aspartate aminotransferase (AST) rise in rhabdomyolysis. Propofol infusion syndrome – an uncommon multisystem complication of prolonged or high-dose propofol administration – may also feature liver injury, and is another differential to be considered in the intensive care unit.

Work-up and prognostication

A thorough drug history is very important in the work-up of DILI. This should include all medicines taken in the 3–6 months prior to the identification of liver injury so as not to miss a delayed onset drug reaction. Reduced consciousness and confusion, common in the intensive care unit, can make information gathering challenging. Family, friends and their GP practice should be consulted, with further attempts to take a drug history from the patient if their consciousness improves.

While many medicines can cause a small and benign rise in liver enzyme levels, DILI should be suspected with large, persistent or unexpected rises. An important step in the workup of any liver injury is to categorize the pattern of biochemical derangement. One useful quantitative approach is to calculate an *R* factor, which uses ALT and ALP values to differentiate hepatocellular, cholestatic, and mixed liver injury (a number of online calculators are freely available). The *R* factor can then be used to guide and prioritize investigations: for example, abdominal imaging may take higher priority in a cholestatic injury, while a viral hepatitis screen may take priority in a hepatocellular injury. Because certain drugs are more commonly associated with specific injury patterns, this information can also be used to begin assessing the likelihood that a particular drug is the cause of a suspected DILI. Information on hepatotoxic substances and typical patterns of injury can be found in online databases such as LiverTox.[16]

Detailed assessment of potential culprit drugs can be made with the Roussel Uclaf Causality Assessment Method (RUCAM), though this is in more routine use among hepatologists than intensivists.[15] King's College Criteria (KCC) can be used to prognosticate and identify early deterioration, particularly in paracetamol toxicity, but also in other ALF aetiologies. There are numerous other scoring systems that incorporate various clinical and biochemical biomarkers in ALF, though encephalopathy and coagulopathy are often prominent factors.[14] No predictive model is definitive, and early involvement of hepatology and transplant teams is recommended for all severe cases of DILI.[15] Table 2 summarizes use cases for different scoring tools relevant to the investigation and prognostication of liver injury and failure.

Drugs associated with DILI

Paracetamol hepatotoxicity is the most common cause of DILI in many parts of the world, and while most cases can be managed without high-level supportive care, progression to ALF necessitates admission to an intensive care unit.[17] Idiosyncratic DILI accounts for the majority of drug-induced, non-paracetamol ALF; antimicrobials are commonly implicated (particularly antituberculosis regimens, sulfonamides, nitrofurantoin and azole antifungals), as are complementary and alternative medicines such as herbal and weight loss supplements. The latter have increased markedly as contributors in recent decades, necessitating explicit enquiry about the use of non-prescribed drugs, supplements, and herbal remedies in the approach to any patient with acute liver injury or failure.[15]

Among commonly encountered antimicrobials in critical care, β-lactams – though particularly for β-lactamase inhibitors present in combined formulations such as co-amoxiclav and piperacillin–tazobactam – more often cause cholestatic or mixed patterns of liver injury.[18,19] However, hepatocellular

Scoring tools commonly used in the workup of liver injury or failure

Tool/metric	Use
R factor	Standardized evaluation of liver injury pattern (hepatocellular, cholestatic, mixed)
Roussel Uclaf Causality Assessment Method (RUCAM)	Standardized evaluation of likelihood of specific drugs as causal of a liver injury
King's College Criteria (KCC)	Prognostication in paracetamol-induced and other aetiologies of ALF (different criteria); early recognition of patients likely to require liver transplant
Model For End-Stage Liver Disease (MELD)	Predicts mortality in cirrhosis/chronic liver failure; more accurate than Child—Pugh. Sometimes used in ALF/ACLF but may be less reliable than KCC especially for paracetamol-induced ALF

Table 2

injury can occur, especially with delayed presentation after drug cessation, which is not uncommon. Mild ALP rises are common with these medicines and can be benign, but should be monitored, and large rises or the development of hepatocellular injury should prompt urgent reassessment and consideration of treatment switching.

Anti-epileptic medicines are a potential cause of hepatotoxicity in intensive care settings. For example, sodium valproate-associated DILI can present with marked hyperammonaemia and encephalopathy, though valproate can also cause these independently of liver injury. Hepatotoxicity can sometimes lead to rapidly progressive liver failure and, if suspected, valproate should be stopped promptly and specialist advice sought to guide starting an appropriate alternative agent.[20] L-carnitine is sometimes administered as an adjunct in valproate hepatotoxicity and hyperammonaemia, though the evidence base is heterogeneous and its use should be under experienced specialist guidance.[21]

Another drug group with growing relevance are immune checkpoint inhibitors (ICIs) — increasingly used in oncology — which can cause DILI in 5—30% of users.[22] This can be asymptomatic, and is most often hepatocellular, idiosyncratic, and immune-mediated. Involvement of the treating oncology team is important in suspected cases, with dedicated severity-based algorithms used to guide decisions around ICI discontinuation and the use of immunosuppressants.

A further consideration specific to anaesthesia and perioperative care is hepatitis associated with halogenated volatile anaesthetics. While halothane-associated hepatitis has become rarer with declining use, modern alternatives (e.g. sevoflurane, isoflurane, desflurane) have very infrequently been linked to cases of idiosyncratic liver injury.[23] When this occurs, the clinical course can be severe, with rapid progression to hepatic necrosis and fulminant liver failure: possibly more so on re-exposure. Awareness of this rare diagnosis remains important when evaluating unexplained perioperative liver failure.

General management principles

In the majority of DILI cases, the mainstay of treatment is withdrawal of the suspected offending drug, even if the diagnosis is not certain, accompanied by supportive care and careful monitoring for evidence of progression to ALF. For paracetamol toxicity, NAC is an effective antidote (discussed further below), however NAC can also sometimes be considered in non-paracetamol DILI progressing to mild ALF, or severe ALF in children.[17] Certain immune-mediated or hypersensitivity-type DILIs can benefit from corticosteroids or other immunosuppressants, however decisions regarding these should be in accordance with locally relevant guidance, and ideally under expert hepatology or other relevant specialist advice (e.g. oncology for immune checkpoint inhibitor associated DILI). As with other causes of ALF, transplant remains the last line of therapy, but for any severe cases, early referral to or consultation of transplant services is recommended.

An update on the management of paracetamol toxicity

Paracetamol (acetaminophen) toxicity remains one of the most common causes globally of acute liver injury and acute liver failure, particularly in Western Europe and North America.[24] Toxicity occurs when a significant quantity of paracetamol is bioactivated to N-acetyl-p-benzoquinone imine (NAPQI), which covalently conjugates with glutathione. This typically occurs in overdose, but can occur at licensed doses if other 'safe' routes of metabolism (sulphation and glucuronidation) become saturated. When glutathione stores are depleted, free NAPQI can cause oxidative hepatocyte damage and necrosis.[25,26] NAC therapy replenishes glutathione stores and thus reduces hepatotoxicity.[27]

Management of paracetamol overdose relies on timely risk stratification, early initiation of NAC, and dynamic re-assessment to guide decisions on stopping treatment or escalation to specialist liver care or transplant centres. This section discusses guidelines for the management of paracetamol toxicity in adults, though much also applies to children over the age of 6.

N-acetylcysteine infusion

A 21-hour, three-bag NAC infusion protocol is licensed by both the UK's Medicines and Healthcare products Regulatory Agency (MHRA) and the USA's Food and Drug Administration (FDA). More recently, the FDA licensed a slightly shorter 20-hour, two-bag infusion with apparently similar efficacy,[28] while a shortened 12-hour, two-bag regimen is endorsed for use off-label by the Royal College of Emergency Medicine and National Poisons Information Service in the UK.[29] The latter regimen, known as the Scottish and Newcastle Anti-emetic Pre-treatment for Paracetamol Poisoning (SNAP) protocol, appears to reduce the risk of NAC side effects — especially anaphylactoid reactions — without adversely affecting liver outcomes.[30] The regimen used should be dictated by local and national guidelines or advice from poison information services.

Treatment is recommended for all individuals with serum paracetamol concentration above the treatment line on a paracetamol nomogram. While multiple versions exist, this commonly extrapolates a 150 mg/litre level at 4 hours post-ingestion (100 mg/litre in the UK). NAC should be started empirically when the nomogram cannot be applied (e.g. staggered overdose, unknown time of ingestion) or when there is evidence of hepatotoxicity in the context of suspected excess paracetamol exposure (e.g. high ALT/INR).

Anaphylactoid reactions to N-acetylcysteine

Anaphylactoid reactions are so named because they often share some features with anaphylactic reactions: angio-oedema bronchospasm, urticaria, flushing, and tachycardia.[31] Hypotension is usually not a feature. Reactions are dose-related, and therefore usually occur during or shortly after the first (higher dose) NAC infusion, especially with regimens that use a fast (e.g. 15-minute) rate for the first bag. Because these are not true allergic hypersensitivity reactions, their implications and management differ from that of anaphylaxis. They can usually be managed with immediate but temporary cessation of NAC infusion, an H1 antihistamine and, if bronchospasm occurs, nebulized salbutamol.[32] Restarting NAC is important, though this is often done at a slower rate.

Indications for treatment continuation or care level escalation

As with other causes of acute liver injury, paracetamol-induced acute liver injury, can interfere with acid–base homeostasis, resulting in metabolic acidosis; impair hepatic synthesis of clotting factors, leading to coagulopathy; and be complicated by acute kidney injury, depletion of hepatic glycogen stores with consequent hypoglycaemia, and elevated serum lactate levels. Guidance typically recommends biochemical monitoring of liver function, renal function, venous lactate and bicarbonate levels, and INR in addition to paracetamol levels. Guidance on the timing and cutoffs for blood markers varies, so local policies should be consulted for specifics. As described above, KCC can be used to predict the need for liver transplant, but typically the following are predictors of poor prognosis and warrant discussion with specialist poison or liver transplant services (reproduced from TOXBASE):[33]

- arterial pH less than 7.3 or bicarbonate less than 18 mmol/litre, despite fluid resuscitation
- INR greater than 3.0 on day 2 or greater than 4.0 thereafter
- oliguria and/or acute kidney injury
- altered level of consciousness
- hypoglycaemia
- elevated lactate (>4 mmol/litre) despite fluid resuscitation.

Beyond NAC infusion and supportive care, transplant is the only available treatment option. Around one in three patients with paracetamol-induced ALF will either die or require transplant.[24]

Conclusion

The safe use of medicines in critically ill patients with liver dysfunction requires an appreciation of both normal hepatic drug handling, and the ways this can be modified by the sometimes profound and often rapidly evolving physiological perturbations seen in critical illness and liver failure. Alterations in hepatic blood flow, enzyme activity, protein binding, and various other factors can each independently, and synergistically, modify drug exposure and effects. Ultimately, prescribing in the context of liver dysfunction requires a nuanced approach that integrates pharmacological principles with clinical judgement and an appreciation of dynamic disease states. Through developing these skills, clinicians may better anticipate altered drug responses, recognize toxicity earlier, and make more informed decisions around drug selection, dosing, and monitoring in patients with liver disease.

Declaration of generative artificial intelligence (AI) and AI-assisted technologies in the manuscript preparation process

Generative AI (ChatGPT) was used to assist the drafting and editing of this manuscript, including to help devise article structure, identify pertinent literature, and summarize guideline advice and discrepancies. All scientific claims and original references have been reviewed by the article's authors, who take full responsibility for its content. ◆

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