

Can paracetamol (acetaminophen) be administered to patients with liver impairment?

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Although 60 years have passed since it became widely available on the therapeutic market, paracetamol dosage in patients with liver disease remains a controversial subject. Fulminant hepatic failure has been a well documented consequence of paracetamol overdose since its introduction, while short and long term use have both been associated with elevation of liver transaminases, a surrogate marker for acute liver injury. From these reports it has been assumed that paracetamol use should be restricted or the dosage reduced in patients with chronic liver disease. We review the factors that have been purported to increase risk of hepatocellular injury from paracetamol and the pharmacokinetic alterations in different pathologies of chronic liver disease which may affect this risk. We postulate that inadvertent under-dosing may result in concentrations too low to enable efficacy. Specific research to improve the evidence base for prescribing paracetamol in patients with different aetiologies of chronic liver disease is needed.

Introduction

'The oft-cited warning that drugs known to produce hepatic injury should not be given to patients with liver disease has little foundation in fact' – Hy Zimmerman, 1999.

Paracetamol, (also known as acetaminophen, N-acetyl-p-aminophenol or APAP) is a commonly used mild analgesic and antipyretic available in numerous prescription and over-the-counter formulations. It is considered a first line analgesic for many patients with chronic liver disease (CLD), primarily due to concern about the side effects of non-steroidal anti-inflammatory (NSAID) and opioid-derived agents [2, 3]. However its association with alanine transaminase (ALT) elevation, considered a surrogate marker for liver injury, has led to uncertainty about its safety margin in patients with pre-existing liver disease [4].

While the use of liver function tests (LFTs) and other surrogate markers for clinical outcomes are often required, ALT in particular as a surrogate marker of liver injury is problematic as this enzyme fluctuates throughout the day in healthy individuals, in relation to exercise, concurrent intake of vitamins and some medications [5]. It is also

upregulated in other disease states such as diabetes and heart failure [5]. Therefore minor transient elevations have not been strongly correlated with hepatotoxicity. This is in contrast to the very high transaminase concentrations seen in patients with drug induced liver injury (DILI). Case reports of DILI in people using 'therapeutic' doses of paracetamol are predominantly in patients who are heavy drinkers, fasting, malnourished, underweight or have concurrent febrile illness [6–14]. We have not found any case reports of hepatotoxicity secondary to therapeutic doses of paracetamol in adults with pre-existing CLD who did not have at least one of these risk factors. One large systematic review inclusive of over 40 000 patients found that the rate of increased serum transaminases and hepatotoxicity was higher in retrospective studies compared with prospective trials, suggesting that some retrospective cases may have been accidental overdoses [15].

While it is noteworthy that a double-blind, two period crossover study of 20 patients with chronic stable liver disease (eight with cirrhosis) tolerated paracetamol at a dosage of 4 g day⁻¹ for 13 days without adverse effects [16], there is a general lack of prospective long term studies examining its use in CLD. The limited evidence base in

addition to the complex pharmacokinetics and pharmacodynamics within the heterogeneous CLD group has contributed to inconsistent paracetamol dosage recommendations of varying magnitude, frequency and daily maximum for acute and chronic pain. Reluctance to prescribe the standard dose of paracetamol may result in poorer efficacy and accelerate progression to alternative analgesics which have well-documented side effects in CLD [2, 17].

For ethical reasons it is unlikely that any large randomized controlled trial (RCT) will be undertaken to understand paracetamol dose–response behaviour in liver disease, and therefore prescribing advice must be extrapolated from a combination of existing pharmacokinetic/pharmacodynamic data, simulated populations, surrogate and actual observed clinical outcomes. We therefore sought to review existing literature for evidence of pharmacokinetic alterations and paracetamol toxicity in different CLD aetiologies, to identify the limitations in the research and to make better-informed recommendations on prescribing paracetamol in CLD.

The evolution of paracetamol in clinical care

Phenacetin and acetanilide, two aniline derivatives with analgesic and antipyretic properties, were first described by Harmon Morse in 1878 and Cahn & Hepp in 1886, respectively [18, 19]. Both were much later found to be prodrugs for the active compound N-acetyl-p-aminophenol [20–24]. The drug was given the approved name ‘paracetamol’ in 1957 and has been included in the published British Pharmacopoeia since 1963 [25].

In the early 1970s the US Food and Drug Administration (FDA) outlined a safe adult dosage of up to 1000 mg every 4–6 h, not to exceed 4000 mg day^{−1}, for no longer than 10 days. The recommendation was based primarily on animal toxicology data, one bioavailability study ($n = 15$ healthy adult males) and four Industry sponsored placebo-controlled post-partum analgesia trials that investigated single dose efficacy over 4–6 h in 338 women ($n = 112$ paracetamol 1000 mg; $n = 113$ paracetamol 650 mg; $n = 113$ placebo) [26–28].

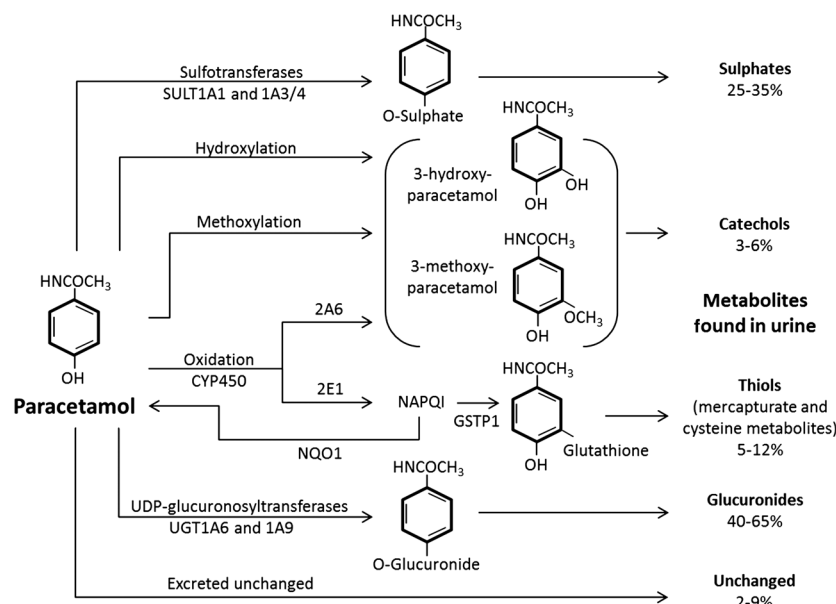
While most of the original data remains unpublished, the efficacy of this dosing regimen has subsequently been supported by clinical trials in a plethora of indications and extensive post-marketing experience. Single dose trials and one large meta-analysis inclusive of over 4000 patients have demonstrated that paracetamol dosed at 1000 mg provides superior analgesia compared with 650 mg [27, 29], 500 mg [30–33] and placebo [27, 29, 34], but no less improvement than 2000 mg [35]. Supra-therapeutic doses of up to 8 g daily in healthy adults and 6 g daily in stroke patients have been shown

to be relatively safe when used for up to 3 days [36, 37], although one case of chronic use at 6 g daily for 14 years has been associated with the later development of cirrhosis [38]. Long term safety data indicated no adverse clinical or biochemical effects in 1039 individuals taking paracetamol 1950–4000 mg daily for up to 1 year [39] or 178 patients taking 2600 mg day^{−1} of paracetamol for 2 years in osteoarthritis trials [40].

Pharmacokinetics and metabolism

Paracetamol is almost completely metabolized by the liver. Pharmacology studies in healthy young men and women suggest that only a very small amount (2–9%) of paracetamol is excreted unchanged [36, 41]. The remainder undergoes phase 1 sulphation predominately via SULT1A1 and SULT1A3/4 [42], glucuronidation predominantly via UGT1A6 and UGT1A9 [43, 44] and oxidation via the cytochrome P450 system (Figure 1). Glucuronide and sulphate conjugates are non-toxic, inactive and readily excreted in the bile (minor) and urine (major) [42]. Phase 1 oxidation via CYP2E1 and CYP2A6 results in the production of thiol and catechol metabolites, respectively [36]. Isoenzymes CYP3A4 and CYP1A2 have been theorized to play a role in paracetamol metabolism based on data from *in vitro* studies. However a human model has found their involvement to be negligible compared with 2E1 [45]. The thiol produced via 2E1, N-acetyl-p-benzoquinone imine (NAPQI), is a reactive oxidative intermediate that has been linked to hepatocellular injury due to its radical affinity and covalent binding to cysteine molecules on liver proteins [42]. Under most circumstances a healthy liver is equipped to detoxify NAPQI by phase 2 conjugation with glutathione (GSH) spontaneously and possibly via glutathione-S-transferase pi 1 (GSTP1) to form inert mercapturate and cysteine metabolites [42]. Alternatively NAPQI may be reduced back to paracetamol via NAD(P)H quinone oxidoreductase 1 (NQO1) [46–48].

Where creatinine clearance may be used to guide dose moderation in patients with renal insufficiency, the Child–Pugh and Model for End Stage Liver Disease (MELD) classification systems for liver disease severity cannot be used to predict changes in drug clearance. Furthermore, pharmacokinetic changes, whilst theoretically predictable, do not always translate into clinically significant toxicity. Several small studies have shown that the excretion of paracetamol in patients with CLD (mild, moderate and severe liver disease including hepatitis C, primary biliary cirrhosis and alcoholic cirrhosis) is slower than in healthy adults with a half-life approximately 1–2 h longer [49–53]. Existing biotransformation studies in this group are sparse (Table 1) although they indicate that paracetamol does not accumulate in CLD despite a higher plasma concentration [51]. Theoretically this increased exposure may correspond with greater efficacy, but this has not been studied. The proportion

**Figure 1**

Pathways of paracetamol metabolism. GSTP1 glutathione-s-transferase pi 1; NQO1 NAD(P)H quinone oxidoreductase 1

Table 1

Half-life (h $\pm$ SD) and 24 h metabolite recovery (as % of dose $\pm$ SD) following a single dose of paracetamol

Study	Sample size	Paracetamol	Glucuronide	Sulphate	Thiol	Half-life ($t_{1/2}$)
Forrest <i>et al.</i> [50]	Control $n = 8$	3.7 ± 0.2	54 ± 1.4	33 ± 1.2	8.6^*	2.4 ± 0.2
	Mild CLD $n = 8$	2.7 ± 0.3	59 ± 2.3	29 ± 1.9	8.7^*	2.2 ± 0.5
	Severe CLD $n = 7$	4.6 ± 0.8	50 ± 3.7	35 ± 3.1	8.4^*	$4.3 \pm 1.2^\ddagger$
Critchley <i>et al.</i> [54]	Control $n = 10^\dagger$	3.6 ± 0.4	59.0 ± 1.0	28.8 ± 1.2	8.5^*	2.3 ± 0.1
	Ethanol $n = 10^\dagger$	7.0 ± 2.1	58.1 ± 2.4	32.2 ± 1.3	$2.8^{*\S}$	2.6 ± 0.1
Leung <i>et al.</i> [55]	Control $n = 26$	4 ± 2	58 ± 10	31 ± 9	7^*	–
	Hepatitis B with cirrhosis $n = 39$	5 ± 2	58 ± 9	28 ± 7	10^*	–
	HCC $n = 19$	4 ± 2	$42 \pm 13^\ddagger$	32 ± 11	22^{***}	–
Zapater <i>et al.</i> [51]	Control $n = 7$	1.2 ± 0.6	59.9 ± 4.2	27.9 ± 4.4	9.7 ± 2.2	$2.0 \pm 0.4^\dagger^\ddagger$
	Mild-Moderate CLD $n = 9$	1.6 ± 1.2	57.1 ± 7.6	30.4 ± 7.1	9.0 ± 2.8	3.7 ± 1.3
	Severe CLD $n = 5$	1.0 ± 0.5	53.5 ± 7.4	35.4 ± 7.9	9.2 ± 4.4	4.0 ± 0.6
Gelotte <i>et al.</i> [53]	Control $n = 12$	$2.4 \pm 0.8^\S$	$49.0 \pm 7.4^\S$	$22.4 \pm 7.0^\S$	$5.5 \pm 2.1^\S$	2.8 ± 1.4
	Mild-Moderate CLD $n = 12$	2.9 ± 2.0	40.2 ± 13.3	27.4 ± 12.0	6.8 ± 2.5	3.4 ± 1.1

*cysteine and mercapturate metabolites were reported separately, but are added here. † In a cohort study, participants (healthy adults $n=5$; heavy drinkers $n=5$) received paracetamol alone at baseline and then paracetamol with ethanol 1 week later. The authors reported similar metabolism between groups and therefore combined them. ‡ half-life in severe disease significantly greater than mild disease and control subjects ($P < 0.001$). § glucuronide conjugates significantly reduced compared with control and hepatitis B groups ($P < 0.001$). ** significant increase in thiol metabolites compared with control and hepatitis B groups ($P < 0.0001$). *** half-life significantly less in control subjects compared with liver disease (combined mild-moderate and severe) ($P = 0.01$). §§ Mean data from 11 participants due to sampling error.

of thiol metabolites also appears to remain unchanged with increasing severity of disease [51, 52, 54–56], suggesting that the presence of liver disease alone may not increase exposure to NAPQI and therefore does not increase risk of toxicity. It should be noted that these studies did not specifically address paracetamol metabolism in the setting of fatty liver disease or obesity, which are known to affect pharmacokinetics variably [57].

Paracetamol toxicity

Side effects with paracetamol when it is used appropriately both short and long term in a healthy adult are very rare. A review of eight observational studies has suggested a dose–response increase in all-cause mortality, cardiovascular, renal and gastrointestinal adverse events for people taking therapeutic doses of paracetamol, although half of the studies did not adjust for concomitant NSAID use [58]. In excess, paracetamol is known to

have a broad toxic spectrum ranging from nausea and anorexia to severe liver damage and death as the sulphation pathway becomes acutely saturated [59] and NAPQI is produced in excess. The sulphhydryl donor N-acetylcysteine (NAC), which serves as a precursor for glutathione and hence speeds the detoxification of NAPQI in this setting, is the only approved agent on the market for treatment of paracetamol overdose [42, 60, 61]. Early diagnosis, modern medicine and use of NAC have considerably improved outcomes for patients who present early with toxicity [42, 60, 61].

While many of the first liver toxicity reports did not adequately report dose, involved large drug quantities or standard doses at what is now understood to be an inappropriate frequency, these cases nevertheless raised the concern that paracetamol should preferably be avoided or the dose reduced in patients with liver disease. This fear was compounded in 2006 when a RCT reported a statistically significant rise in ALT in healthy adult volunteers [62], the majority of whom were Hispanic, following 14 days of paracetamol administration (dosed at 1 g every 4–6 h) with or without co-administration of an opioid (morphine, hydromorphone or oxycodone). ALT reached three times the upper limit of normal (ULN) in 41 of 106 paracetamol-treated patients (39%) and none of 39 placebo-treated subjects, irrespective of opioid. However, 8 years later the methodology and results of the study by Watkins *et al.* [62] have been challenged by an investigation [63] which demonstrated the time course of aminotransferase fluctuation in 205 healthy adult volunteers administered the same regimen of paracetamol over at least 16 days. In contrast to the earlier report, only three patients had an ALT greater than three times the ULN during the course of the study while 77% ($n = 157$) either had no ALT elevation or a minor elevation that resolved (ALT returned to $<ULN$) by day 16. The investigators followed 47 of the remaining 48 patients whose ALT persisted above 47 U L^{-1} at day 16. They continued to consume paracetamol until LFTs returned to normal. All but one patient (postulated to be due to systemic infection) had resolution by day 40. It has been suggested [63] that had the Watkins *et al.* [62] study protocol permitted data collection beyond 14 days and not discontinued treatment in patients with transaminases $>$ three times the ULN, ALT may have returned to baseline. Indeed, given no patient exhibited clinical signs of toxicity in the Watkins *et al.* [62] paper, is possible that the ALT rise may have been a result of an interacting ethnic genetic variability in metabolism and was likely to be of little clinical significance [64–67]. Transient elevation of liver transaminases is not uncommon with numerous medications, including statins and some antibiotics, and marginal ALT elevations in patients who are institutionalized for studies have also been

linked to institutionalization, not necessarily treatment intervention [68].

Nevertheless, the conservative recommendations that followed the publication of the Watkins *et al.* [62] paper made by leading bodies of ‘at risk’ populations persist. For example, the American Liver Foundation recommended patients not exceed 3 g of paracetamol daily and the American Geriatric Society suggested no more than 2–3 g daily in older patients with hepatic insufficiency or a history of alcohol abuse. McNeil Laboratories self-initiated packaging changes to recommend a 3 g daily maximum on their Tylenol products, and the FDA’s pursuit to discourage prescribers from recommending products that contain more than 325 mg paracetamol per dosage unit is ongoing. It must be noted that these generalized recommendations may not be applicable to all patients, and sub-therapeutic dosing may accelerate progression to stronger analgesics.

Glucuronidation capacity

Most glucuronosyltransferases enzymes (UGTs) can metabolize paracetamol and unlike sulphotransferase enzymes, glucuronidation is a non-saturable pathway [43, 69]. A study of repeated paracetamol dosing at 4 g, 6 g and 8 g daily over 3 days in 24 healthy young men and women of normal weight has demonstrated a higher concentration of the glucuronide conjugate and a lower concentration of sulphate and thiol conjugates than was anticipated from single dose data, suggestive of time-dependent changes in paracetamol metabolism [36, 70]. As paracetamol may induce UGT1A6 [36], chronic ingestion may reduce exposure to the reactive intermediate in healthy adults, as a greater proportion of the drug is metabolized via the non-toxic phase 1 glucuronidation pathway. However, extrapolating these data into the CLD population is difficult as some metabolic pathways are variably up- or down-regulated according to disease aetiology and severity, discussed in the Section entitled “Drug Interactions and Other Confounding Factors”.

Glutathione depletion

Detoxification of NAPQI by conjugation with hepatic glutathione may be impaired in the setting of malnutrition, recent fasting or advanced cirrhosis wherein the synthesis of glutathione may be impaired [71]. Therefore these patients may theoretically be at higher risk of paracetamol toxicity. A number of small studies in healthy adults have indicated that nutritional deficiency decreases availability of glutathione precursors in muscle and plasma [72], reduces free glutathione but not total glutathione concentrations in the plasma [73] and decreases synthesis rate but not concentration of glutathione in red blood cells [74]. A diet high in dairy products has been positively correlated with glutathione

concentrations in the brain [75]. Numerous pathways involved in the regulation of glutathione concentrations may be affected by the presence of liver disease, although the majority of studies have been performed in animal models [76].

Reduced glutathione concentrations and reduction in the GSH : GSSG ratio are suggestive of oxidative stress, reflecting reduced hepatic capacity to recover from insult [77]. Measurement of human hepatic glutathione is achievable only through invasive tissue biopsy and thus is difficult to study on a large scale. Hepatic and peripheral plasma glutathione concentrations are correlated in rats [78, 79] and humans with various liver diseases [80, 81]. Following paracetamol administration, a reduction in glutathione stores of at least 70% was required before liver damage became evident in mice [60], although no such study has been performed in humans. One study in alcoholic patients found that the median plasma glutathione concentration was not related to paracetamol intake, although a statistically significant inverse correlation was found between γ -glutamyl transferase (GGT) and plasma glutathione [82].

Irrespective of causation, a plethora of studies have shown plasma and hepatic glutathione concentrations to be variably reduced or unchanged in patients with diverse liver diseases as outlined in Table 2 [71, 83–94]. Although reduction of glutathione concentrations has been demonstrated in most liver disease aetiologies, there has been no change demonstrated in the ratio of thiol metabolites retrieved in urine, nor evidence of liver injury in these patients. Thus, in the absence of contributory factors, such as malnutrition, there is no strong evidence of impaired glutathione conjugation in CLD and therefore it is unlikely that glutathione store depletion alone increases risk of hepatotoxicity in the clinical setting. Indeed, case reports published on hepatotoxicity secondary to therapeutic doses of paracetamol [6, 11, 14] are often in severely underweight, malnourished or fasting patients suggesting that acute nutritional deficiency is likely a more important consideration than underlying liver disease when considering paracetamol for these patients.

Ethanol consumption

There have been a handful of cases of hepatotoxicity following self-reported therapeutic doses of paracetamol in heavy drinkers [10, 95]. Irrespective of their body mass index, alcohol-dependent subjects are frequently malnourished [96] affecting glutathione availability. Ethanol is also an inducer of CYP2E1, the same enzyme that produces the toxic metabolite NAPQI. Significant CYP2E1 induction measured using the chlorzoxazone test was demonstrated in healthy male volunteers within 1 week of consuming 40 g of ethanol per day and

continued to increase for at least 4 weeks while ethanol consumption remained constant [97]. However, as ethanol is a competitive substrate for the enzyme and also a stimulator of NQO1 [47, 98–100], concurrent intake of ethanol and paracetamol has actually been shown to reduce paracetamol-induced toxicity in mice [47, 101, 102] and rats [99, 103] and has been associated with a decrease in the elimination of thiol metabolites in humans [55, 100]. Furthermore, concurrent acute alcohol ingestion with paracetamol overdose appears protective against hepatotoxicity irrespective of paracetamol dose [104].

However there is an increased risk of NAPQI formation during the acute alcohol withdrawal phase, as 2E1 activity can take between 3 to 8 days to return to normal [97, 105]. Without a competitive substrate, production of thioether metabolites has been shown to transition from suppressed to over-expressed within 8 h of ethanol cessation [106]. While small, single dose studies have reported conflicting results of unchanged or increased production of thiol metabolites in heavy drinkers with or without cirrhosis who consumed paracetamol within 48 h of ethanol cessation [106, 107], stronger evidence from a number of RCTs has demonstrated that paracetamol ingestion during this 'high risk' withdrawal period does not predispose patients to liver injury [66, 90, 108–110], as summarized in Table 3. A meta-analysis of published RCTs inclusive of 551 paracetamol-treated heavy drinkers vs. 350 placebo-treated heavy drinkers found no significant evidence of ALT elevation from baseline to day 4 [111].

It would thus appear that paracetamol is relatively safe to use in the average heavy drinker (who is not malnourished and either has no cirrhosis or early compensated cirrhosis) at doses up to 4 g daily when clinically indicated for short periods of time, but the lack of data in decompensated alcoholic liver disease (ALD) makes dosing recommendations difficult in this group. While 3–4 g daily may be reasonable short term for acute pain, a maximum daily dose of 2–3 g in alcoholic cirrhosis may be a safer recommendation if analgesia is required for more than 14 days [112]. Definitive evidence to guide recommendations here is lacking, and alternative analgesics also have relative contraindications.

Non-alcoholic liver diseases

Paracetamol has been studied in small groups of adults with liver disease of various aetiologies at different stages of disease progression (Table 4). The drug has similar metabolism and elimination without clinical or biochemical signs of accumulation or toxicity following both single and repeated dosing for up to 2 weeks [16, 50–53, 113], but there are scant quality prospective studies to support its use beyond this time frame. There

Table 2

Hepatic tissue and plasma glutathione concentrations in liver disease

Study	Sample measured	Control	Liver disease	Data as mean $\pm$ 95% CI	P
Burgunder & Lauterburg [82]	Plasma GSH (mean $\pm$ SD $\mu\text{mol l}^{-1}$)	9.3 $\pm$ 2.4 (n = 8)	3.6 $\pm$ 1.1 (alcoholic cirrhosis n = 8)	Control 9.3 $\pm$ 2.0 Alcoholic cirrhosis 3.6 $\pm$ 0.9	P < 0.001
	Total GSH (mean $\pm$ SD $\mu\text{mol l}^{-1}$)	16.6 $\pm$ 6.2 (n = 8)	7.1 $\pm$ 2.6 (alcoholic cirrhosis n = 8)	Control 16.6 $\pm$ 5.2 Alcoholic cirrhosis 7.1 $\pm$ 2.2	P < 0.002
Altomare et al. [83]	Tissue GSH (mean $\pm$ SEM $\mu\text{mol g}^{-1}$ liver)	4.14 $\pm$ 0.1 (n = 15)	2.77 $\pm$ 0.1 (NALD* n = 20)	Control 4.14 $\pm$ 0.2 NALD* 2.77 $\pm$ 0.2	P < 0.001
			2.55 $\pm$ 0.1 (ALD n = 35)	ALD 2.55 $\pm$ 0.2	P < 0.001
Bianchi et al. [70]	Plasma GSH (mean $\pm$ SD $\mu\text{mol l}^{-1}$)	5.91 $\pm$ 1.04 (n = 6)	1.69 $\pm$ 1.06 (alcoholic and HCV cirrhosis n = 10)	Control 5.91 $\pm$ 1.09 Alcoholic and HCV cirrhosis 1.69 $\pm$ 0.76	Not significant
Bernhard et al. [84]	Plasma GSH (mean $\pm$ 95%CI $\mu\text{mol l}^{-1}$)	14.1 $\pm$ 1.3 (n = 19)	12.5 $\pm$ 1.6 (chronic hepatitis C n = 36)	Control 14.1 $\pm$ 1.3 Chronic hepatitis C 12.5 $\pm$ 1.6	Not significant
Van de Castele et al. [85]	Whole blood GSH (mean $\pm$ SEM $\mu\text{mol l}^{-1}$)	908 $\pm$ 43 (n = 21)	952 $\pm$ 71 (alcoholism without cirrhosis n = 14)	Control 908 $\pm$ 90 Alcoholism without cirrhosis 952 $\pm$ 153	Not significant
			823 $\pm$ 51 (alcoholic cirrhosis Child-Pugh A n = 9)	Alcoholic cirrhosis Child-Pugh A 823 $\pm$ 118	Not significant
			909 $\pm$ 91 (alcoholic cirrhosis Child-Pugh B n = 5)	Alcoholic cirrhosis Child-Pugh B 909 $\pm$ 253	Not significant
			500 $\pm$ 71 (alcoholic cirrhosis Child-Pugh C n = 18)	Alcoholic cirrhosis Child-Pugh C 500 $\pm$ 150	P < 0.05
			520 $\pm$ 90 (non-alcoholic cirrhosis Child-Pugh C n = 6)	Non-alcoholic cirrhosis Child-Pugh C 520 $\pm$ 231	P < 0.05
Saricam et al. [86]	Erythrocytic GSH (mean $\pm$ SD nmol g ⁻¹ Hb)	56.90 $\pm$ 5.03 (n = 16)	34.09 $\pm$ 2.19 (NAFLD n = 26)	Control 56.90 $\pm$ 2.68 NAFLD 34.09 $\pm$ 0.88	P < 0.001
Cemek et al. [87]	Whole blood GSH (mean $\pm$ SD mg dl ⁻¹)	34.38 $\pm$ 1.41 (n = 29)	3.89 $\pm$ 1.59 (acute hepatitis A n = 19)	Control 34.38 $\pm$ 0.54 Hepatitis A 3.89 $\pm$ 0.77	P < 0.001
Czeczot et al. [88]	Tissue GSH (mean $\pm$ SD $\mu\text{mol mg}^{-1}$ protein)	5.52 $\pm$ 3.27 (n = 15)	4.62 $\pm$ 2.94 (HCC n = 15)	Control 5.21 $\pm$ 1.81 HCC 4.62 $\pm$ 1.63	P < 0.05
			3.45 $\pm$ 2.11 (cirrhosis n = 15)	Cirrhosis 3.45 $\pm$ 1.17	P < 0.05
Kuffner et al. [89]	Plasma GSH (mean $\pm$ SD $\mu\text{mol l}^{-1}$)	2.17 $\pm$ 0.97 (n = 56)	2.27 $\pm$ 0.85 (alcoholic patients, day 3 of detox while taking paracetamol n = 56)	Control 2.17 $\pm$ 0.26 Alcoholics taking paracetamol 2.27 $\pm$ 0.23	Not significant
		1.90 $\pm$ 0.68 (n = 23)	2.02 $\pm$ 0.74 (alcoholic patients, day 3 of detox while taking placebo n = 23)	Control 1.90 $\pm$ 0.29 Alcoholics taking placebo 2.02 $\pm$ 0.32	Not significant
Lee et al. [90]	Blood GSH (mean $\pm$ SD $\mu\text{mol l}^{-1}$)	1294.3 $\pm$ 258.0 (n = 137)	970.5 $\pm$ 321.7 (virus-originated HCC n = 24)	Control 1294.3 $\pm$ 43.6 Virus-originated HCC 970.5 $\pm$ 135.8	P < 0.001
	Blood GSH : GSSG ratio (mean $\pm$ SD)	20.3 $\pm$ 10.2 (n = 137)	6.7 $\pm$ 4.6 (virus-originated HCC n = 24)	Control 20.3 $\pm$ 1.7 Virus-originated HCC 6.7 $\pm$ 1.9	P < 0.001
	Tissue GSH (mean $\pm$ SD $\mu\text{mol l}^{-1}$ g ⁻¹ protein)	723.6 $\pm$ 215.0 (adjacent cancer-free tissue n = 24)	439.8 $\pm$ 198.4 (virus-originated HCC n = 24)	Control 723.6 $\pm$ 90.8 Virus-originated HCC 439.8 $\pm$ 83.8	P < 0.001
	Tissue GSH : GSSG ratio (mean $\pm$ SD)	10.5 $\pm$ 3.7 (adjacent cancer-free tissue n = 24)	4.4 $\pm$ 1.9 (virus-originated HCC n = 24)	Control 10.5 $\pm$ 1.6 Virus-originated HCC 4.4 $\pm$ 0.8	P < 0.001
Das et al. [91]	Tissue GSH (mean $\pm$ SD $\mu\text{g mg}^{-1}$ protein)	4.08 $\pm$ 0.59 (n = 38)	3.64 $\pm$ 0.19 (NAFLD n = 35)	Control 4.08 $\pm$ 0.19 NAFLD 3.64 $\pm$ 0.07	P < 0.01
			3.19 $\pm$ 0.58 (ALD n = 38)	ALD 3.19 $\pm$ 0.19	P < 0.001
Narasimhan et al. [92]	Age adjusted whole blood GSH (mean $\pm$ SD $\mu\text{mol g}^{-1}$ Hb)	7.5 $\pm$ 1.4 (n = 50)	6.2 $\pm$ 1.3 (NAFLD without T2DM n = 50)	Control 7.5 $\pm$ 0.40 NAFLD without T2DM 6.2 $\pm$ 0.37	P < 0.05
			4.0 $\pm$ 1.5 (NAFLD with T2DM n = 50)	NAFLD with T2DM 4.0 $\pm$ 0.43	P < 0.001
			5.2 $\pm$ 1.5 (T2DM without NAFLD n = 50)	T2DM without NAFLD 5.2 $\pm$ 0.43	P < 0.05
Kaffe et al. [93]	Whole blood GSH (Median [range] $\mu\text{mol l}^{-1}$)	1101 [276-5409] (n = 50)	475 [4-2743] (AIC n = 49)	–	P $\leq$ 0.001
			495 [4-2743] (AIC without cirrhosis n = 43)	–	P $\leq$ 0.01
			209 [89-659] (AIC with cirrhosis n = 6)	–	P $\leq$ 0.001
		1135 [293-5409] (n = 41)	512 [51-5541] (AIH n = 36)	–	P $\leq$ 0.01
			511 [88-2977] (AIH without cirrhosis n = 26)	–	P $\leq$ 0.01
			293 [51-5541] (AIH with cirrhosis n = 10)	–	P $\leq$ 0.001

95% CI were calculated from original data in all studies except Bernhard et al., to facilitate comparison between studies. *NALD (non-alcoholic liver disease) group included patients with chronic active hepatitis n = 7; chronic persisting hepatitis n = 3; steatosis n = 2; and cirrhosis n = 8. AIC, autoimmune cholestatic liver disease; AIH, autoimmune hepatitis; ALD, alcoholic liver disease; GSH, glutathione; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; P = significance vs. control group; T2DM, type 2 diabetes mellitus.

Table 3

Controlled paracetamol consumption in chronic alcoholic patients

Study	Ethanol intake	Paracetamol	Control	Duration	Result
Kuffner <i>et al.</i> [108]	Admission to alcohol detoxification facility, CAGE and MAST screen. Intake ceased during study.	1 g four times daily (<i>n</i> = 102)	Placebo (<i>n</i> = 99)	2 days (additional 2 days monitoring)	No significant difference in AST, ALT or INR
Kuffner <i>et al.</i> [89]	Positive alcohol on breathalyzer, CAGE and MAST screen. Intake ceased during study.	1 g four times daily (<i>n</i> = 258)	Placebo (<i>n</i> = 114)	3 days (additional 2 days monitoring)	No significant difference in AST, ALT, bilirubin or INR
Heard <i>et al.</i> [65]	Healthy volunteers who consume 1 to 3 alcoholic beverages daily. Intake continued throughout study.	1 g four times daily (<i>n</i> = 100)	Placebo (<i>n</i> = 50)	10 days (additional 1 day monitoring)	Mean ALT increased by 8.7 U l^{-1} in treatment group on day 11 ($P = 0.04$). No significant change in AST, INR or bilirubin
Bartels <i>et al.</i> [109]	>6 drinks daily for >6 weeks. Alcohol consumption ceased 12 to 72 h prior to enrolment. Intake ceased during study.	1.3 g every 8 h (<i>n</i> = 18)	Placebo (<i>n</i> = 17)	11 doses (5 days total monitoring)	Serum α -GST significantly lower on day 2 ($P = 0.017$) and day 3 ($P = 0.02$) in treatment group. No difference in ALT, AST or INR
Dart <i>et al.</i> [107]	Current drinking episode of ≥ 7 days. Intake ceased during study.	1 g four times daily (<i>n</i> = 74)	Placebo (<i>n</i> = 68)	5 days (additional 2 days monitoring)	Mean ALT increased by 11.7 U l^{-1} in treatment group ($P = 0.04$). No significant change in AST, INR or bilirubin

Table 4

Controlled paracetamol consumption in other chronic liver diseases

Study	Liver disease	Paracetamol	Control	Duration	Result
Benson <i>et al.</i> [15]	ALD (<i>n</i> = 6), Laennec's cirrhosis (<i>n</i> = 4), post-necrotic cirrhosis (<i>n</i> = 1), chronic active hepatitis (<i>n</i> = 6), chronic persistent hepatitis (<i>n</i> = 4), primary biliary cirrhosis (<i>n</i> = 2) and unspecified cirrhosis (<i>n</i> = 1)	1 g four times daily (<i>n</i> = 20)	Placebo (<i>n</i> = 20)	13 day crossover (13 days paracetamol, 13 days placebo)	No significant change in bilirubin, ALP, AST or ALT
Dargère <i>et al.</i> [112]	Chronic HCV	1 g three times daily (<i>n</i> = 17)	Placebo (<i>n</i> = 17)	7 days (additional 3 days monitoring)	No change in ALT or viral load
Dart <i>et al.</i> [107]	Alcoholics with HCV	1 g four times daily (<i>n</i> = 24)	Placebo (<i>n</i> = 26)	5 days (additional 2 days monitoring)	No significant change in ALT, AST, INR or bilirubin

appears to be no significant increase in excretion of thiol metabolites, indicating production of NAPQI is not amplified in mild, moderate or severe liver disease [51, 52, 54]. Similarly, two studies in patients with compensated and decompensated cirrhosis (total *n* = 549, including alcohol-related liver disease, chronic hepatitis C infection and cryptogenic cirrhosis) admitted to tertiary care facilities found that use of over-the-counter analgesia including paracetamol was not associated with hospitalization for liver-related events, while frusemide, lactulose and alcohol consumption were positively related [114, 115]. Of 45 patients treated for chronic active hepatitis, there were no differences in LFTs or disease manageability between 17 patients who were taking paracetamol prior to admission and those who were not [116]. However,

cumulative paracetamol intake $\geq 7.5 \text{ g}$ in the days prior to admission has been found to decrease prothrombin index and factor V activity, and increase bilirubin in acute viral hepatitis, specifically hepatitis A [117].

Recognition of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) is relatively new. Hence there are a lack of patient data in this group. Despite evidence of increased NQO1 activity in NAFLD and NASH [118], a review of paracetamol-induced liver injury in seven rodent models of obesity and NAFLD suggested a similar or increased risk of toxicity compared with controls [119]. Patients with pre-existing NAFLD without cirrhosis were reported to have a higher risk of acute liver injury (OR 7.5) following paracetamol overdose [120]. Obese patients without fatty liver disease

have similar or reduced risk of severe acute liver injury following paracetamol overdose compared with non-obese patients, although obese patients who developed acute liver failure had poorer outcomes [121, 122]. There are no clinical studies of pharmacokinetics in paracetamol dosing in adults with NAFLD or data on long term therapeutic use.

Drug interactions and other confounding factors

During the progressive stages of liver disease xenobiotic metabolism is altered with significant overall reduction of CYP450 enzymes [123]. NQO1 protein expression and activity has been shown to increase in NASH and NAFLD, while activity of GST, UGT and SULT are variably dysregulated [118, 124]. Glutathione peroxidase, reductase and transferase activity is regulated differently and inconsistently in NAFLD, ALD, cirrhosis and hepatocellular carcinoma [89, 92] and glutathione stores are also altered (Table 2). The clinical consequence of these alterations on paracetamol metabolism in patients with these liver diseases has not been studied.

Increased protein expression and activity of CYP2A6 has been reported in patients with progressive NAFLD, hepatitis, primary biliary cirrhosis and alcoholic cirrhosis [125–128]. However increase in catechol metabolite production has not been demonstrated, suggesting that paracetamol metabolism via this pathway is not necessarily affected in these disease states.

CYP2E1 function appears to remain preserved despite reduced protein expression in progressive NAFLD [128]. Similarly, activity remains unchanged while disease remains mild or compensated. In contrast, activity decreases with worsening disease (Pugh score > 6, Child Class B or C) and in cholestatic cirrhosis [123, 129]. While this may suggest that NAPQI formation will be reduced in decompensated cirrhosis or in people with cholestatic liver disease, this has not been studied.

It has been proposed that direct and indirect drug interactions may affect risk of paracetamol toxicity by moderation of the CYP450 isozyme system or changes to gastric emptying. Induction of 2E1 by isoniazid has been well-documented, but studies in healthy volunteers have shown that isoniazid may inhibit NAPQI formation as a competitive substrate for the enzyme in much the same way as alcohol [130, 131]. Other small studies on enzyme inducers such as phenobarbital, phenytoin, rifampicin, omeprazole and carbamazepine have suggested that their effect on 2E1 is not significant, and thus they are unlikely to be responsible for excessive NAPQI formation when taken concurrently with paracetamol [45, 132, 133].

Some guidelines recommend that adult patients of low body weight (<50 kg) receive a reduced maximum daily dose of paracetamol (15 mg kg⁻¹ four times a day) [134]. However weight as an independent risk factor

for paracetamol toxicity, in the absence of chronic disease and malnutrition, has not been well studied.

Prescribing in other groups

The complex pharmacokinetic–pharmacodynamic relationship of drug–patient and drug–disease interactions causes debate around appropriate paracetamol prescribing in children, older persons and some other chronic disease states. Metabolism and clearance of paracetamol in the healthy elderly population has been found to be comparable with young adults, though persons over 80 years have a greater overall exposure following intravenous administration [135–138]. One study has demonstrated an increase in glucuronide conjugates in 12 male children with NAFLD, but no significant changes in terms of clearance, half-life, AUC or C_{max} [139]. The nature of the pain being treated should also be taken into consideration regardless of population, as recent evidence suggests paracetamol used in patients (aged 45 ± 16 years) without CLD may be no better than placebo for acute low back pain [140].

Future research

A helpful future study would be a large, long term (> 1 month) prospective observational study of CLD patients with need for therapeutic analgesia, to provide correlation data between dose, concentration, efficacy and toxicity with paracetamol. This will improve dose guidance for individual patients. Furthermore, whilst glutathione content has been relatively well-examined in numerous hepatic diseases, there remains scant knowledge of enzyme dysregulation (including CYP, UGT, SULT, NQO1) in most CLD aetiologies. Further research in the latter area will assist with development of recommendations regarding paracetamol dosing.

It is noted that one of the mechanisms of action of paracetamol is an inhibitory effect on COX enzymes, which may be linked to long term renal and cardiovascular outcomes. While this review has primarily focussed on the need for studies on hepatic toxicity with normal dosing in liver disease, studies on cardiovascular health with paracetamol are also needed.

Conclusion

Recent reviews have concluded that paracetamol is a safe and effective first line agent in almost all patients regardless of liver disease aetiology. Although the need for dose reduction in the healthy population seems largely unnecessary, it may be warranted in certain severe or decompensated hepatic disease states, particularly if patients are malnourished, are not eating or have a dry weight less than 50 kg. Whilst a cautious and conservative approach

has previously been recommended for all CLD patients, prescribers should be encouraged to consider appropriate dosing for each individual patient, taking into account their underlying disease state and the pharmacological covariates.

As the prevalence of lifestyle related liver diseases such as ALD and NAFLD is likely to increase over the coming decades, it is important that clinicians are able to use existing analgesics safely and effectively. To that effect, studies aimed at improving our understanding of changes to paracetamol metabolism, efficacy and toxicity will be invaluable.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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