Outcomes from massive paracetamol overdose: a retrospective observational study

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STRUCTURED SUMMARY

AIM

Treatment of paracetamol (acetaminophen) overdose with acetylcysteine is standardised, with dose determined only by patient weight. The validity of this approach for massive overdoses has been questioned. We systematically compared outcomes in massive and non-massive overdoses, to guide whether alternative treatment strategies should be considered, and whether the ratio between measured timed paracetamol concentrations ($APAP_{pl}$) and treatment nomogram thresholds at those time points ($APAP_t$) provides a useful assessment tool.

METHODS

Retrospective observational study of all patients (n=545) between 2005-2013 admitted to a tertiary care toxicology service with acute non-staggered paracetamol overdose. Massive overdoses were defined as extrapolated 4-hour plasma paracetamol concentrations >250mg/L, or reported ingestions ≥30g. Outcomes (liver injury, coagulopathy and kidney injury) were assessed in relation to reported dose and $APAP_{pl}$:$APAP_t$ ratio (based on a treatment line through 100mg/L at 4 hours), and time to acetylcysteine.

RESULTS

Ingestions of ≥30g paracetamol correlated with higher peak serum aminotransferase (r=0.212, *P*<0.0001) and creatinine (r=0.138, *P*=0.002) concentrations. Acute liver injury, hepatotoxicity and coagulopathy were more frequent with $APAP_{pl}$:$APAP_t$ ≥3 with odds ratios (OR) and 95% confidence intervals (CI) of 9.19 (5.04-16.68), 35.95 (8.80-158.1) and 8.34 (4.43-15.84),

respectively (P<0.0001). Heightened risk persisted in patients receiving acetylcysteine within 8 hours of overdose.

CONCLUSION

Patients presenting following massive paracetamol overdose are at higher risk of organ injury, even when acetylcysteine is administered early. Enhanced therapeutic strategies should be considered in those who have an $APAP_{pl}$:$APAP_t$ ≥3. Novel biomarkers of incipient liver injury and abbreviated acetylcysteine regimens require validation in this patient cohort.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Acetylcysteine protocols in paracetamol overdose were initially developed empirically, with subsequent validation using pharmacokinetic studies of non-toxic doses in healthy individuals.
- It is unclear whether these modelling assumptions are robust in massive overdoses.
- Case reports suggest that such patients may have worse outcomes, and biochemical data hint at the need for supplemental acetylcysteine.

WHAT THIS STUDY ADDS

- Patients with an $APAP_{pl}$:$APAP_t$ ≥3 (based on a treatment line through 100mg/L at 4 hours) have higher rates of organ injury.
- Excess risk persists even with acetylcysteine administration within 8 hours of overdose.

- Patients with massive overdoses may benefit from higher or protracted doses of acetylcysteine, or approaches to enhance gastrointestinal drug elimination.

TABLE OF LINKS

LIGANDS
paracetamol

This Table lists key ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1].

Introduction

Paracetamol overdose remains the commonest drug overdose, and cause of acute liver failure, in Europe, Australia and North America [2, 3] Intravenous acetylcysteine is the mainstay of treatment and an effective antidote if used early in the course of poisoning [3, 4]. The decision to treat acute, non-staggered, paracetamol overdose is principally based on measured plasma paracetamol concentrations, taken at least 4 hours after ingestion [3]. International guidelines differ in their recommendations as to threshold paracetamol concentrations for treatment on nomograms, but once these have been exceeded acetylcysteine dosing regimens are very similar throughout the world [5]. The dose of acetylcysteine is determined only by patient weight, and does not vary according to other factors including the dose of paracetamol taken, plasma paracetamol concentration, time to presentation, and/or co-ingestion of other drugs.

Acetylcysteine regimens have never been subject to definitive dose-ranging studies in humans, nor have different regimens been compared in randomised controlled trials sufficiently powered to inform on the optimal strategy for preventing hepatotoxicity. As a result, current guidelines still advocate treatment principally based on the dose calculated in the 1970s for the initial studies of acetylcysteine in paracetamol toxicity [4]. At this time, there were few data to inform on appropriate dosing, and much of the initial work was empirical. It had, however, been established that hepatic and renal toxicity were mediated through formation of N-acetyl-p-benzoquinone imine (NAPQI), once paracetamol conjugation through glucuronidation and sulphation had been saturated [6]. NAPQI can be detoxified to cysteine and mercapturate conjugates by glutathione, with organ injury resulting once stores of the latter become

deplete [7]. Consequently, pharmacokinetic studies were performed in healthy individuals to determine the level of glutathione depletion over a range of paracetamol concentrations, and a dose of acetylcysteine selected that would match this on a stoichiometric basis [5, 7].

Whilst this standard treatment regimen has proven extremely successful, the "one size fits all" approach has been criticized [5, 8, 9]. In particular, it is not clear whether the modelling assumptions underlying the initial acetylcysteine dose calculations hold true with very large overdoses, and whether therapy could be better tailored to individual cases in these situations [10, 11]. Several case reports, and one recent observational study, highlight adverse outcomes in patients with massive paracetamol overdoses despite early acetylcysteine [12-16]. Such patients have higher cysteine and mercapturate to glucuronide conjugate ratios, implying increased proportions of paracetamol undergoing conversion to NAPQI and consistent with the need for supplemental acetylcysteine beyond that suggested by the original models [6]. The aims of this study were to evaluate the development of organ injury in massive overdoses in a systematic manner, compare this to non-massive ingestions, and assess whether reported ingested dose or the ratio of the measured plasma paracetamol concentration ($APAP_{pl}$) to the corresponding treatment nomogram paracetamol concentration threshold at that time ($APAP_t$) provided superior prediction of outcome. We assessed all patients presenting to a specialist toxicology service with acute paracetamol overdose meeting criteria for treatment with acetylcysteine, and determined outcomes for those taking massive overdoses.

Methods

Patients and clinical data

Clinical data on all patients presenting to our large inner-city hospital with toxicology-related problems are prospectively entered into a purpose-designed clinical database, with follow-up to the end of the acute inpatient admission episode [17]. Data were extracted for all individuals who had taken an acute, single (non-staggered) overdose of paracetamol in whom the time of ingestion was recorded, and who received treatment with acetylcysteine, between May 2005 and May 2013. There are no universally agreed criteria of what constitutes a massive paracetamol overdose; we therefore defined this pragmatically as an extrapolated 4-hour plasma paracetamol concentration >250mg/L (2.5-fold the current UK threshold requiring treatment with acetylcysteine), or (where plasma paracetamol concentrations were not available) if a patient reported ingestion of ≥30g paracetamol. Caldicott and Ethical Approval are in place for the database; data for this study were analysed anonymously and therefore no further ethical approval was required. This manuscript is written in compliance with STROBE guidelines.

The following information was extracted from the database: basic demographic data; time of presentation to the emergency department; reported quantity and time of paracetamol ingested; plasma paracetamol concentration ($APAP_{pl}$) and time (t) this blood test was performed relative to exposure; time to initiation of acetylcysteine; and peak serum aminotransferase concentration, international normalized ratio (INR) and serum creatinine occurring on admission or during the course of treatment. Calculated 4-hour plasma paracetamol concentrations were back-extrapolated from measured values using

the formula used in previous studies: $APAP_{pl}/2e^{-(0.693/4)t}$ [18]. We also calculated the ratio between $APAP_{pl}$ and the threshold concentration at that time point on the treatment nomogram (based on a line through 100mg/L at 4 hours) above which acetylcysteine would be administered ($APAP_t$).

Treatment regimens during study period

In the UK prior to 2012, single (non-staggered) paracetamol overdoses were treated with acetylcysteine if measured plasma paracetamol concentrations were above a nomogram line starting at 200mg/L at 4 hours if deemed standard risk, or 100mg/L at 4 hours if high risk (for example, patients with chronic alcohol misuse, medical conditions associated with glutathione depletion, and/or taking cytochrome P450-2E1 inducing medication). The standard acetylcysteine protocol was 150mg/kg over 15 minutes, followed by 50mg/kg over 4 hours, and finally 100mg/kg over 16 hours. From 2012, UK guidelines changed such that everyone was treated according to the 100mg/L at 4 hours nomogram threshold line, with the duration of the first dose of acetylcysteine extended to 1 hour [19]. With both of these regimens, after completion of the third infusion, renal function, liver function and coagulation parameters are rechecked, and a further 16 hour acetylcysteine infusion instituted in the event of any significant derangement [20].

Assessment of organ injury

There are a number of different working definitions for liver injury based on rises in serum alanine or aspartate aminotransferase concentrations, and data for all of the following were considered: 1. paracetamol-related liver injury,

defined by a rise ≥2-fold the upper limit of normal (ULN; the threshold above which UK guidelines recommend extending the acetylcysteine course) [8]; 2. drug-induced acute liver injury, defined as ≥3-fold ULN [16, 21]; and 3. paracetamol-related hepatotoxicity, with aminotransferase concentrations >1,000IU/L [4, 15, 22]. Coagulopathy was defined as an INR rising above 1.3 (the threshold that would prompt extension of acetylcysteine therapy) [23], and significant acute kidney injury as a serum creatinine >150μmol/L (in the absence of pre-existing chronic kidney disease) [24]. In addition, current UK guidelines advocate consideration for liver transplantation in paracetamol overdoses with an INR >6.5 or serum creatinine >300μmol/L [23].

Statistical analysis

Data are expressed as median (interquartile range), unless otherwise stated, and were analysed using GraphPad Prism (version 7.0; GraphPad Software, CA, 2016). All eligible patients within the specified time frame were included in the study, and no formal power calculation was performed. Continuous variables were compared using the Mann-Whitney U-test, correlation by Spearman rank coefficient, and event frequencies by Fisher's exact test. A P value ≤0.05 was considered significant. Analyses did not impute missing data.

Results

Patient and overdose characteristics

A total of 545 patients fulfilled the inclusion criteria. Median age was 31 (22-43) years, and 341 (62.6%) patients were female. Median time from overdose to presentation was 3h25min (1h44min-6h47min). Plasma paracetamol

concentrations were available in 529 (97%) patients; in four individuals the samples had haemolysed and were not repeated, and in twelve individuals they were not performed. Median plasma paracetamol concentration was 119mg/L (66-182), and time from exposure to measurement was 5h47min (4h36min-9h5min). The median extrapolated 4-hour concentration was 190.0 (126.8-273.5) mg/L.

Reported ingested dose of paracetamol

The reported ingested dose was recorded in 520 (95.4%) cases, with a median of 16 (12.5-25) grams. One hundred and four patients (20.0%) took a dose ≥30g, and the maximum ingested dose was 141g. Reported ingested doses correlated with extrapolated 4-hour plasma concentrations (r=0.367, P<0.0001; Figure 1a).

$APAP_{pl}$:$APAP_t$ ratios

Ratios were calculated in 527 (96.7%) patients; in the remainder this was not possible either due to lack of a measured plasma paracetamol concentration (n=4) or due to late presentation beyond the time limits of treatment nomograms (n=14). The median ratio was 1.94 (1.30-2.77). This measure correlated strongly with 4-hour extrapolated plasma concentrations (r=0.999, P<0.0001), and moderately with reported dose (r=0.368, P<0.0001; Figure 1b).

Prevalence of organ injury

Peak serum aminotransferase concentrations, INR and creatinine results were available in 538, 540 and 542 patients, respectively. One hundred and seventeen (21.5%) patients had peak serum aminotransferase concentrations >2-fold ULN;

69 (12.8%) >3-fold ULN; and 20 (3.7%) >1,000 IU/L. Forty-nine (9.1%) had a peak INR >1.3; and 2 (3.7%) >6.5. Nine (1.7%) had significant acute kidney injury with a creatinine >150μmol/L, and 4 (0.7%) >300μmol/L. Fifty-three (9.7%) patients received additional acetylcysteine beyond the standard regimen. All patients recovered from the acute episode of poisoning, except for one individual who presented 13h8min after reported ingestion of 24g paracetamol and ethanol, and developed chronic renal impairment requiring long-term renal replacement therapy. This patient also had acute liver failure with a serum aminotransferase concentration of 8,509 IU/L and INR of 3.32, although hepatic function subsequently recovered and was normal at the time of hospital discharge. No patients died as a result of the acute episode of poisoning.

Relationship between estimates of overdose and development of organ injury

Patient demographics described by nomogram group (according to extrapolated 4-hour plasma paracetamol concentrations) are shown in Table 1. Correlations between reported ingested dose, 4-hour extrapolated plasma paracetamol concentrations, $APAP_{pl}$:$APAP_{t,}$ and the various outcome measures were assessed (Table 2). Sensitivities, specificities, positive predictive values, and odds ratios for different $APAP_{pl}$:$APAP_{t}$ thresholds for identifying serum aminotransferase rises >2-fold ULN (promoting extended acetylcysteine infusion) are reported in Table 3.

Relationship to reported ingested dose of paracetamol

Reported ingested dose correlated with peak serum aminotransferase concentrations (r=0.212, *P*<0.0001; Figure 2a) and creatinine (r=0.138, *P*=0.002; Figure 2b), but not INR (r=0.034, p=ns; Figure 2c). Median peak serum aminotransferase concentration was 23IU/L (16.75-39.25) in patients reporting overdoses under 30g, and 29IU/L (22-73) in those who had taken ≥30g (*P*=0.001). Reported dose did not reliably differentiate the different grades of liver injury (Figure 2d). Median INR was 1.1 in both patients taking ≥30g paracetamol and also those reporting non-massive overdoses (IQR 1.02-1.18 and 1.03-1.19, respectively). Median serum creatinine was 65μmol/L (57-75) in patients reporting ingestions <30g and 72.5μmol/L (63.25-82.75) in those who reported ingestion of ≥30g (*P*<0.0001), but there was no difference in the frequency of creatinine rises over 150μmol/L (<30g, n=5; ≥30g, n=3) or 300μmol/L (<30g, n=1; ≥30g, n=2) between these groups.

Relationship to $APAP_{pl}$:$APAP_t$

$APAP_{pl}$:$APAP_t$ ratio correlated with peak serum aminotransferase concentration (r=0.286, *P*<0.0001; Figure 3a), INR (r=0.314, *P*<0.0001; Figure 3b) and creatinine concentration (r=0.090, *P*=0.04; Figure 3c). There were associations between increasing $APAP_{pl}$:$APAP_t$ and liver injury (Figure 4a-c), coagulopathy (Figure 4d) and acute kidney injury. A ratio ≥3 was associated with an OR of 7.15 (4.20-12.06; *P*<0.0001) for peak serum aminotransferase concentrations >2-fold ULN; 9.19 (5.04-16.68; *P*<0.0001) for acute liver injury; 35.95 (8.80-158.1; *P*<0.0001) for hepatotoxicity; 8.34 (4.43-15.85; *P*<0.0001) for coagulopathy; and 4.69 (1.38-15.44; *P*=0.03) for acute kidney injury.

Correspondingly, values for $APAP_{pl}$:$APAP_t$ ratios ≥6 were 13.93 (6.24-31.79; *P*<0.0001) for aminotransferase rises >2-fold ULN; 15.94 (6.97-35.32; *P*<0.0001) for acute liver injury; 44.64 (15.0-121.5; *P*<0.0001) for hepatotoxicity; 13.59 (5.84-32.33; *P*<0.0001) for coagulopathy; and 10.65 (2.75-39.12; *P*=0.008) for acute kidney injury.

Time to acetylcysteine and outcomes

Median time to acetylcysteine was 8h30min (6h24min-12h36) in male patients and 7h42min (6h0min-10h18min) in female patients (*P*=0.03). Time to treatment correlated with serum aminotransferase concentration (r=0.168 *P*=0.0002), INR (r=0.153, *P*=0.0006) and serum creatinine (r=0.087, *P*=0.05).

We subsequently restricted analyses to the 248 patients who received acetylcysteine within 8 hours of reported paracetamol ingestion (Table 4). The association between reported ingested dose and serum aminotransferase concentration persisted (r=0.153, *P*=0.02), as did those between $APAP_{pl}$:$APAP_t$ and serum aminotransferases or INR. An $APAP_{pl}$:$APAP_t$ ≥3 remained predictive of organ injury with an OR of 5.25 (1.98-13.13; *P*=0.002) for aminotransferase rise >2-fold ULN; 4.70 (1.66-14.48; *P*=0.02) for acute liver injury; ∞ (3.56-∞; *P*=0.01) for hepatotoxicity; and 5.21 (1.60-18.3; *P*=0.02) for coagulopathy.

By comparison, in patients who received acetylcysteine later than 8 hours from reported ingestion, $APAP_{pl}$:$APAP_t$ ≥3 had an OR of 8.61 (3.90-18.23; *P*<0.0001) for aminotransferase rises >2-fold ULN; 11.38 (4.91-25.36; *P*<0.0001) for acute liver injury; 18.88 (4.73-84.67; *P*<0.0001) for hepatotoxicity; and 9.46 (4.00-21.29; *P*<0.0001) for coagulopathy.

Discussion

Although the current regimen of acetylcysteine for treating paracetamol overdose has been extremely successful, the continued use of a standard protocol for every case has been questioned [5, 8, 9]. In particular, it has been suggested that patients who have taken very large overdoses may require higher doses of acetylcysteine, or protracted infusions. Intravenous doses up to 980mg/kg acetylcysteine over 48 hours have previously been used safely [25], notwithstanding evidence from one animal model that suggested prolonged therapy might delay recovery from hepatotoxicity [26]. It is known that NAPQI generation rises with increasing paracetamol dose, and also that hepatic injury prolongs paracetamol half-life. Furthermore, there are several case reports, and one observational study, of patients developing hepatotoxicity despite receiving acetylcysteine within 8 hours of reported overdose [12-16].

Our study systematically assessed outcomes of massive paracetamol overdose. Key findings were that, despite receiving standard therapy with acetylcysteine, patients with massive overdoses were more likely to develop significant liver and kidney injury, and coagulopathy. $APAP_{pl}$:$APAP_{t}$ ratio was a better predictor of organ toxicity than the reported dose ingested. Although overall correlations with outcomes were modest in magnitude, and differences in medians (while statistically significant) were of limited clinical relevance, this did provide a tool for distinguishing higher and lower risk groups. This persisted even when acetylcysteine was administered within 8 hours of reported ingestion, demonstrating that while time to treatment was a strong predictor of organ injury it was not the sole determining factor in early presenting poisoning. These findings validate and extend, in an independent cohort, those recently

published by a specialist toxicology unit in Edinburgh [16]. The case features in our patients were broadly similar, except that liver injury and hepatotoxicity were more frequent in the highest concentration subgroups in our study; this may relate to the higher measured paracetamol concentrations at the times of presentation.

The original acetylcysteine treatment regimen was constructed based on empirical considerations [4, 7]. Although effective for the majority of patients, it is not clear that the implicit assumptions necessarily hold true in massive overdose. In such patients, absorption of paracetamol may be delayed: this could be due to direct effects of paracetamol on gastric motility [27]; co-ingestion of other drugs such as opiates or anticholinergics that delay gastric emptying [28]; insufficient volume of gastric secretions to solubilize large quantities of paracetamol [29]; or formation of a pharmacological bezoar [13]. The half-life of paracetamol can progressively extend as hepatotoxicity develops, such that significant quantities of NAPQI could be generated after the 16-hour acetylcysteine infusion has finished [30]. Finally, there is evidence from animal models that paracetamol may undergo enterohepatic recirculation, with hydrolysis of non-toxic conjugates by gut flora and reabsorption of the parent drug [31]. These factors likely explain, alone or in combination, the double peaks of plasma paracetamol reported following large overdoses [13]. In some of these patients, the second peak can occur in excess of 30 hours after ingestion, and these individuals are more likely to develop hepatotoxicity despite early acetylcysteine therapy.

While there has been considerable recent interest in the development of novel early biomarkers, such as miRNA-122, to further stratify those at high risk

of tissue injury and guide management, there is a possibility these might fail to identify cases if a major contributor to adverse outcomes in massive paracetamol overdose is a delay in the pharmacokinetic profile [32]. This is also relevant when considering adoption of an abbreviated acetylcysteine protocol [33], and might mandate protracted observation in people who have taken massive doses. It is important that this patient cohort is specifically considered when evaluating proposed changes to practice.

There are a few limitations to the current study. Principal among these is the reliance on an accurate patient history and medical documentation at the time of clinical review, particularly as regards paracetamol dose and time of ingestion. As the database is clinical, there is a risk of misclassification since data are not validated at the time of entry, although one strength of this approach is that data entry is blinded to the study question. The correlations between reported doses, extrapolated 4-hour plasma paracetamol concentrations and $APAP_{pl}$:$APAP_{t}$ provide some reassurance that these possess a reasonable degree of reliability, although concordance was lower than in previously reported series [34] and there were a number of outliers. These could result from errors in patient estimation of dose or calculation by the admitting physician, or by an in increase in the half-life of paracetamol as has been previously documented in patients with significant paracetamol toxicity, thus introducing inaccuracies into extrapolation of paracetamol concentrations. Secondly, blood tests for paracetamol, liver, coagulation and renal function were performed routinely during clinical practice at presentation to the Emergency Department, as well as on completion of the standard acetylcysteine regimen, and were thus not completely systematic. In the absence of more frequent testing it is possible that

in some cases peak values may have been missed. In addition, at our hospital at the time of this study, paracetamol concentrations were not repeated during or after treatment, so it is not possible to comment on alterations in plasma half-life. It was also not possible to formally grade kidney injury using RIFLE/AKIN criteria, due to the lack of baseline blood tests and limited longitudinal follow-up in this patient cohort. Third, prior to 2012, the acetylcysteine protocol required calculations to be performed by both the prescribing physician, as well as the administering nurses. This process is error prone [35], and hence it is possible that some patients nominally receiving early treatment were in fact under-dosed. Finally, the assumptions underlying extrapolation of 4-hour paracetamol concentrations may break down if paracetamol metabolism changes in a non-liner fashion or becomes saturated at very high doses, or should a double peak phenomenon exist widely.

These findings are clinically important, as they suggest that under current protocols patients taking massive paracetamol overdoses may be undertreated, and that either an increase in the dose intensity and/or duration of acetylcysteine therapy could be beneficial. A high $APAP_{pl}$:$APAP_{t}$ ratio is associated with increased risk and therefore further consideration should be given to alternative acetylcysteine treatment strategies in these patients. Risks of organ injury rose with an $APAP_{pl}$:$APAP_{t}$ (based on a treatment line through 100mg/L at 4 hours) ≥3, and a ratio ≥6 was strongly predictive. Based on analysis of the sensitivities and positive predictive values of different threshold ratios, we believe on balance that the former cut-off should be used to define a higher risk group. The optimum strategy is not clear at present, and would require a more detailed understanding of the mechanisms responsible for the

excess in organ injury despite early acetylcysteine. This could be informed by performing serial plasma paracetamol measurements in at-risk individuals to determine whether this relates to delayed absorption, second peaks or prolonged half-life. In the event of a significant contribution from the former, or substantial enterohepatic recirculation of the parent drug, there may also be a role for multiple doses of activated charcoal to augment gastrointestinal elimination. Novel biomarkers of liver injury, and abbreviated treatment protocols, should be specifically validated in this patient cohort.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that PID is a member of the MHRA CHM 2016 Paracetamol Expert Working Group, and DJBM is a consultant for GSK. There are no other relationships or activities that could appear to have influenced the submitted work.

Contributors

PID, DMW and SLG conceived the study; DJBM, CLD and AMD collected data; and DJBM performed statistical analyses. All authors were involved in data interpretation, drafting and critical revision of the manuscript, and have approved the final version submitted for publication.

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544

FIGURE LEGENDS

Figure 1 Correlations between reported dose of paracetamol and ingested and **a)** extrapolated 4-hour plasma paracetamol concentrations and **b)** $APAP_{pl}$:$APAP_t$.

Figure 2 Relationship between reported dose of paracetamol ingested and **a)** serum aminotransferase concentration, **b)** INR and **c)** serum creatinine. **d)** Cumulative frequency of different grades of liver injury with reported dose.

Figure 3 Relationship between $APAP_{pl}$:$APAP_t$ and **a)** serum aminotransferase concentration, **b)** INR and **c)** serum creatinine.

Figure 4 Percentage of patients in each $APAP_{pl}$:$APAP_t$ group with **a)** no liver injury (serum aminotransferase concentrations <50IU/L), **b)** acute liver injury, **c)** hepatoxicity and **d)** coagulopathy.