ORIGINAL RESEARCH

Determinants of drug-induced liver injury following therapeutic use of paracetamol in patients with genetic disorders: A systematic review

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ABSTRACT

Background: Drug-induced liver injury (DILI) is a significant cause of acute liver failure, with paracetamol (APAP) being a common culprit. This systematic review aimed to explore the risk factors associated with DILI following the therapeutic use of APAP in patients with genetic disorders. **Methods**: The protocol was registered with PROSPERO (CRD42023397546). Inclusion criteria encompassed studies reporting on DILI following the therapeutic use of APAP in patients with genetic disorders. A systematic search of EMBASE, PubMed, CINAHL, PsycInfo, grey literature databases, and search engines yielded 13 eligible case reports. Quality and risk of bias were assessed according to established guidelines. Results were synthesized both qualitatively and quantitatively. **Results**: Despite therapeutic dosing, high serum APAP levels and elevated liver function test values were observed which significantly correlated with APAP doses. Genetic polymorphisms in drug-metabolizing enzymes, glutathione deficiency, reduced volume of distribution, and other factors such as concomitant drugs, malnutrition, stress, dehydration, and genetic predispositions may have contributed. Delays in suspecting APAP toxicity and initiating N-acetylcysteine therapy were observed, contributing to severe liver injury. **Conclusions**: Understanding the determinants of DILI in this unique population is crucial to prevent medication errors and enhance patient safety. This study emphasises the need for personalised medicine and pharmacogenetic screening to identify susceptible individuals and guide APAP usage. It underscores the importance of raising awareness, vigilance, using lower doses, therapeutic drug monitoring, and proactive measures for early intervention. Dosage guidelines need to be revised. The main limitation of this study was the bias inherent in case reports.

Keywords: drug-induced liver injury; genetic disorders; medication error; paracetamol; personalised medicine; pharmacogenomics; pharmacokinetics ; risk factors; therapeutic drug monitoring

INTRODUCTION

Drug-induced liver injury (DILI) is a leading cause of acute liver failure (ALF) in both the United States and Western Europe.[1,2] N-acetyl-p-aminophenol (APAP), also known as paracetamol or acetaminophen, is the most frequently reported cause for DILIand the primary cause of ALF.[1–3] APAP is a common household medicine often used for self-medication by children and adults for fever and pain.[4–6] It is particularly valuable for patients in whom aspirin is contraindicated.[7]It is available with[8] and without a prescription,[4–6]and in fixed-dose combinations.[7]

The development of DILI due to APAP ingestion is often associated with acute intentional overdose, resulting in a dose-dependent and potentially fatal hepatic necrosis,[3,7,9] which is the most serious acute adverse drug reaction (ADR) of APAP overdosage.However, even in recommended dosage, in the presence of risk factors, APAP has been found to induce liver injury in both patients and healthy

volunteers.[10,11] In these instances, the intended therapeutic dosage inadvertently transforms into an unintended overdose, a critical yet preventable medication error,[11] and an unforeseen therapeutic misadventure.[3,10]

Of particular interest is the emergence of reports of DILI following the therapeutic use of APAP in patients with genetic disorders.[12–22]Genetics plays a role, to a greater or lesser extent, in all diseases,and our cellular and bodily responses to the environment may differ according to our DNA.[23]Genetic predisposition to DILI is poorly understood.[24] Surprisingly, an initial search of various databases failed to uncoversystematic reviews (SR) or protocols to address this concern in this demographic.

Hence, given the widespread availability and use of APAP and its potential to cause severe liver injury under various circumstances, it is imperative to unravel the interplay between APAP dosage and other factors in causing DILI. Our primary objectivewas to investigate the risk factors associated with DILI resulting from the therapeutic use of APAP in patients with genetic disorders. This study offers a clinical pharmacological perspective,aiming toraise awareness, deepen comprehension, and emphasise the pivotal role of personalised medicine and vigilance in averting such adverse outcomes and bolstering patient safety.

METHODS

The protocol for this SR adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) guidelines.[25]On 18th February 2023, the protocolwas registered with PROSPERO (CRD42023397546). Nosignificant amendments or deviations from the protocol were made.We followed the PRISMA statementreporting guidelines.[26]

Eligibility criteria

The eligibility criteria were designed in the PEO format.Population: Humans, of all ages and genders, with genetic disorders.Exposure: Therapeutic use of APAP. Intentional or accidental overdose cases were excluded, as were cases with concomitant presence of other known causes of liver injury.Outcome: The primary outcome of interest was DILI, as indicated by liver function tests (LFT), APAP levels, or other confirmatory evidence. We excluded cases of liver injury attributed to other factors.Study design: Our SRcentred on case reports with comprehensive individual patient-level data: patient specifications, therapeutic APAP usage, and the reported APAP dosage. Studies lacking adequate data for critical appraisal were excluded.

Information sources

We conducted extensive searches in various bibliographic databases, from inception to31st December 2023. The following sources were explored:Academic databases: EMBASE, PubMed, CINAHL, PsycINFO; Grey literature databases: OpenGrey, Grey Literature Report; Organizational website: AHRQ Patient Safety Network; Search engine: Google Scholar. We searched PROSPERO, Cochrane Library, and JBI Evidence Synthesis databases for any similar protocols or SR. Cross-referencesfrom relevant articles were also examined.

Search strategy

We executed a systematic search without imposing any language or time restrictions. The search strategies used for the two main databases are given below.

EMBASE

1. exp *paracetamol/
2. exp genetic disorder/
3. exp genetic polymorphism/
4. exp genetic predisposition/
5. exp pharmacogenetics/
6. exp "chemical and drug induced liver injury"/
7. exp liver failure/
8. exp liver function test/
9. exp case report/
10. 2 or 3 or 4 or 5
11. 6 or 7 or 8
12. 10 or 11
13. 1 and 12
14. 9 and 13
15. limit 14 to human

PubMed

("Acetaminophen"[MeSH Major Topic] AND ("genetic diseases, inborn"[MeSH Terms] OR "genetic diseases, x linked"[MeSH Terms] OR "genetic diseases, y linked"[MeSH Terms] OR "polymorphism, genetic"[MeSH Terms] OR "Genetic Predisposition to Disease"[MeSH Terms] OR "Pharmacogenetics"[MeSH Terms] OR "Toxicogenetics"[MeSH Terms] OR ("Chemical and Drug Induced Liver Injury"[MeSH Terms] OR "Hepatic Insufficiency"[MeSH Terms] OR "Liver Function Tests"[MeSH Terms]))) AND ((casereports[Filter]) AND (humans[Filter]))

Selection process

We employed Zotero for managing bibliographic references. Reviewers received comprehensive guidance regarding the study screening and selection process. A Zotero group library was created, and all investigators worked independently, posting their comments. Reports in languages other than English were translated using Google Translate, with quality control measures to ensure accuracy. In case of any disagreements, differences were resolved through discussion, with the involvement of a third team member when necessary.

Risk of bias and quality of studies

The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports[27] was used to assess the

quality and risk of bias associated with case reports. Association was reassessed utilizing the Bradford Hill criteria,[28] while causality was evaluated using the Roussel Uclaf Causality Assessment Method (RUCAM),[1] commonly known as the "CIOMS scale" for causality assessment.

To determine whether concomitant drugs posed potential hepatotoxic risks, a comprehensive search was conducted within the British National Formulary (BNF),[9]LiverTox[29] and the Liver Toxicity Knowledge Base (LTKB) of the Food and Drug Administration (FDA).[30]Drugs were subsequently categorized into three groups: those with the highest concern, less concern, and no concern regarding hepatotoxicity. Drug interactions were checked online.[31]

Data collection process

Data extraction and management were carried out using Microsoft Excel. A data extraction form was developed and piloted across selected articles to ensure standardized data collection. The form underwent minor revisions and clarifications before full-scale data extraction commenced.

Data items

Data extracted were synthesized numerically wherever possible. Extracted information included essential study characteristics (authors, publication year, country), patient demographics (age, sex, weight, medical history), exposure details (APAP dosage, duration, administration route), outcome measures (time to onset, APAP serum levels, DILI, LFT), contextual information (concomitant drugs, other relevant risk factors) and management ofDILI.

Definitions and effect measures

Genetic disorders were defined as diseases caused by genetic variants inherited from the parents or acquired de novo.[23] Hepatocellular DILI was defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels exceeding five times the upper limit of normal, or a similar fold increase above the patient's pre-treatment baseline levels when available.[1,24]APAP dosage criteria were adopted from the BNF: maximum recommended dose is 60 mg/kg/day; not to exceed 4g for an adult (0.5 g to 1 g or 15 mg/kg every 4 to 6 hours). Toxicity is considered highly unlikely with daily staggered doses consistently below 75 mg/kg/day, and it rarely occurs within the range of 75 – 150 mg/kg/day. Doses exceeding 150 mg/kg/day carry a risk of serious toxicity.[9]The reference therapeutic plasma levels of APAP,[32]and LFT[1]are displayed in Tables 2 and 3 respectively.

Missing data

In instances of missing data, attempts were made to contact the case study authors for relevant information, but responses were not received. Deleting cases was not a viable option; hence, imputing some values became necessary. In case 1, ALT and the corresponding ALT times values were imputed with the median values. In case 2, a 9-month-old infant, weight was imputed based on age according to WHO growth charts.[33] In case 9, APAP level was imputed with the median value. In case 10, a 26-year-old adult, median weight of all other adult cases was imputed. The overall study results, before and after the imputations,remainedunchanged.

Synthesis methods

Our analysis encompassed both quantitative and narrative synthesis, incorporating a clinical pharmacology perspective.Data were managed and analysed using Microsoft Excel. The Real Statistics Resource Pack software (Release 8.9.1) by Charles Zaiontz (2013 – 2023)[34]aided in the data analysis. When necessary, laboratory values were converted to SI units using the conversion factors outlined in the AMA Manual of Style 11th edition.[35]Descriptive statistics, such as medians and quartiles, were utilized to calculate point estimates, along with 95% confidence intervals, for continuous data. Kendall rank correlation coefficient (Tau, one-tailed) was calculated to assess strength of association between data sets, at an alpha of 0.05.[36]

RESULTS

Study characteristics

Our search (see Figure) yielded 11 articles,[12–22]from which 13 eligible case reports were extracted. Among these (see Table 1) 10 (77%) cases were males and 3 females; 9 (69%)were children, of which 5 were aged 1 year or less. All had genetic disorders; some, such as cleft palate, are multifactorial with a genetic component. They were admitted to hospitals for either elective procedures or emergency treatments for critical illnesses. Baseline ALT levels were available for cases 3, 4 and 11, showing slight elevation. For the remaining cases, ALT levels were either reported as normal or were not available.

Risk of bias and quality of studies

We conducted critical appraisal of the 13 case reportsaccording to JBI guidelines.[27] All cases were reported well and met our predefined eligibility criteria. Some cases had minor missing data items, but this did not impact their eligibility. Regarding theassessment of associationusing the Bradford Hill criteria,[28] a probable causal relationship was observed for APAP, while the association with some concomitant drugs was deemed possible. DILI in all cases was severe and direct (intrinsic), consistent with the RUCAM scale and criteria established by the CIOMS.[1]

APAP Exposure

Most patients (see Table 2) received therapeutic doses of APAP within the hospital setting, primarily for postoperative pain or fever in critical illness. Cases 2 and 8 received APAP outside the hospital

setting.Cases 3, 6, and 12 received doses of APAP that were under 60 mg/kg/day. While some cases received slightly higher doses, all remained below the overdose level of 150 mg/kg/day. Routes of administrationincluded oral (8 cases), rectal (5 cases) and intravenous (4 cases).

Other factors

Concomitant drugs of most concern were carbamazepine (case 4) and amoxicillin-clavulanate (cases 5 and 6), while drugs of lesser concern were general anaesthetics. Otheridentified risk factors included malnutrition, fasting, dehydration, low muscle mass, hypovolemia, hypotension, stress of surgery and critical illness, as well as genetic factors.

Onset and recovery

The onset (see Table 3) was acute. After discontinuing APAP, 11 out of 13 patients recovered, with 8 receiving NAC treatment and 3 recovering without it. Tragically, cases 6 and 11 died despite NAC treatment.

APAP levels

Except cases 2 and 6, APAP blood levels were higher than the therapeutic range (see Table 2). In most cases (except for cases 1, 4, 5), there was considerable delay in measuring APAP levelsafter the cessation of APAP administration. In case 9, APAP levels were not available and the diagnosis of APAP causing ALF was made by exclusion; the patient recovered after cessation of APAP and supportive management.

DILI

All patients in this study exhibited DILI with a rapid onset following the initiation of APAP treatment. Most patients had high APAP levels. ALT and AST (see Table 3) increased bymore than the five times. In case 1, where ALT value was imputed, a very high AST level was observed.Additionally, some cases showed other evidence, such as adducts (cases 5, 6 and 7) and liver biopsyconfirming hepatocellular necrosis (case 10). In case 9, the diagnosis of APAP-induced liver injury was made by exclusion.

Correlations

In our analysis (see Table 4), higher APAP dosage showed a statisticallysignificantcorrelation with faster onset, higher APAP plasma levels, and elevated ALT levels.Moreover, increased APAP plasma levels were significantly associated with faster onset and higher ALT levels.Additionally, a faster onset was significantly correlated with higher ALT levels.

Table1: Patient demographics

Case report	Country	Sex	Age (y)	Weight (kg)	Disease	Admission	Baseline ALT
01. Hynson[12]	Australia	M	12.00	43.00	DMD	ES	NA
02. Tokatli[13]	Turkey	F	0.75	8.20[a]	GSD	CI	NA
03. Pearce[14]	UK	M	42.00	70.00	LGMD	CI	1.3 µkat/L
04. Pearce[14]	UK	M	20.00	45.00	DMD, E	CI	3.92µkat/L
05. Ceelie[15]	Netherlands	F	12.00	40.00	SMA 2	ES	Normal
06. Ceelie[15]	Netherlands	F	17.00	55.00	CMD, CD	CI	Normal
07. Iorio[16]	USA	M	0.67	8.90	CP	ES	NA
08. Bucaretchi[17]	Brazil	M	0.07	3.13	CD	CI	NA
09. Kocaaslan[18]	Turkey	M	1.00	10.00	CP	ES	NA
10. Brehm[19]	Germany	M	26.00	50.00[a]	SMA 3	CI	NA
11. Lao[20]	Norway	M	30.00	50.00	DMD	ES	1.69 µkat/L
12. Yin[21]	UK	M	16.00	50.00	BMD	NG	Normal
13. Raghu[22]	New Zealand	M	0.08	0.96	PDA	ES	NA

Median (Q1, Q3) Age (years): 12 (0.71, 23.00).

[a]Imputed weight; median (Q1, Q3) after imputation: 43.00 (8.55, 50.00); before imputation: 43.00 (8.90, 50.00).

Reference ALT (male): 0.48 – 0.55 µkat/L (29 – 33 U/L).[1]

ALT, alanine aminotransferase; BMD, Becker muscular dystrophy; CD, carnitine deficiency; CI, critical illness; CMD, congenital muscular dystrophy; CP, cleft palate; DMD, Duchenne muscular dystrophy; E, epilepsy; ES, elective surgery; F, female; GSD, glutathione synthase deficiency; LGMD, limb girdle muscular dystrophy; M, male; NA, not available; NG, nasogastric feeding; PDA, patent ductus arteriosus; SMA,spinal muscular atrophy.

Table 2: APAP dosage and plasma levels.

	APAP dosage			APAP levels	
Case report	Days	mg/kg/day	Route	µmol/L	Delay[b]
01. Hynson[12]	6.00	76.16	Rectal	528.00	0
02. Tokatli[13]	2.00	60.00	PO?	6.61	5 d
03. Pearce[14]	4.00	42.86	IV, PO	436.52	8 h
04. Pearce[14]	2.50	88.89	PO	628.33	0
05. Ceelie[15]	3.00	66.67	Rectal	264.56	0

06. Ceelie[15]	11.00	39.67	Rectal	66.14	36 h
07. Iorio[16]	2.50	80.76	Rectal, PO	548.96	1 d
08. Bucaretchi[17]	3.00	60.00	PO	509.28	48 h
09. Kocaaslan[18]	3.00	72.00	Rectal, PO	273.28[a]	NA
10. Brehm[19]	5.00	60.00	IV	145.51	38 h
11. Lao[20]	4.00	72.50	IV, PO	282.00	1 d
12. Yin[21]	4.00	40.00	PO	138.89	6 h
13. Raghu[22]	5.00	60.00	IV	153.00	8 h

[a]Imputed APAP plasma level; median (Q1, Q3) APAP plasma level after imputation: 272.28 (142.20, 518.64); before imputation: 273.28 (140.55, 523.32).
[b]Delay, in hours or days, in APAP plasma level measurement afterdiscontinuation.
Median (Q1, Q3) Days: 4 (2.75, 5); Dose mg/kg/day: 60 (51.43, 74.33).
APAP doses >150 mg/kg/day carry a risk of serious toxicity.[9]
Reference APAP plasmalevel: 66 to 132 µmol/L (10 – 20 µg/mL).[31]
APAP, paracetamol; IV, intravenous; PO, oral.

Table 3: Outcomes

Case report	Onset	APAP levels	ALT		AST		Comments
	Days	µmol/L	µkat/L	Times	µkat/L	Times	
01. Hynson[12]	6	528.00	52.50[b]	95.45[c]	123.20	216.97	No NAC, R
02. Tokatli[13]	7	6.61	23.41	56.08	50.67	89.24	No NAC, R
03. Pearce[14]	4	436.52	63.79	48.97	NA	NA	NAC, R
04. Pearce[14]	1	628.33	64.30	16.38	NA	NA	NAC, R
05. Ceelie[15]	3	264.56	69.69	166.92	41.50	73.09	Adduct, NAC, R
06. Ceelie[15]	11	66.14	14.56	34.88	34.12	60.09	Adduct, NAC, D
07. Iorio[16]	3	548.96	215.18	390.45	407.88	718.35	Adduct, NAC, R
08. Bucaretchi[17]	3	509.28	18.15	32.94	67.45	118.79	NAC, R
09. Kocaaslan[18]	4	273.28[a]	41.20	74.76	15.16	26.71	No NAC, R
10. Brehm[19]	5	145.51	16.70	30.30	NA	NA	Biopsy, NAC, R
11. Lao[20]	4	282.00	148.98	88.33	183.48	323.15	PGT, NAC, D
12. Yin[21]	4	138.89	93.50	169.67	91.82	161.71	NAC, R
13. Raghu[22]	5	153.00	11.07	20.09	16.60	29.24	NAC, R
Median	4.00	272.28	52.50	56.08	59.06	104.01	
Q1	3.00	142.20	17.43	31.62	29.74	52.38	
Q3	5.50	518.64	81.60	131.19	138.27	243.51	

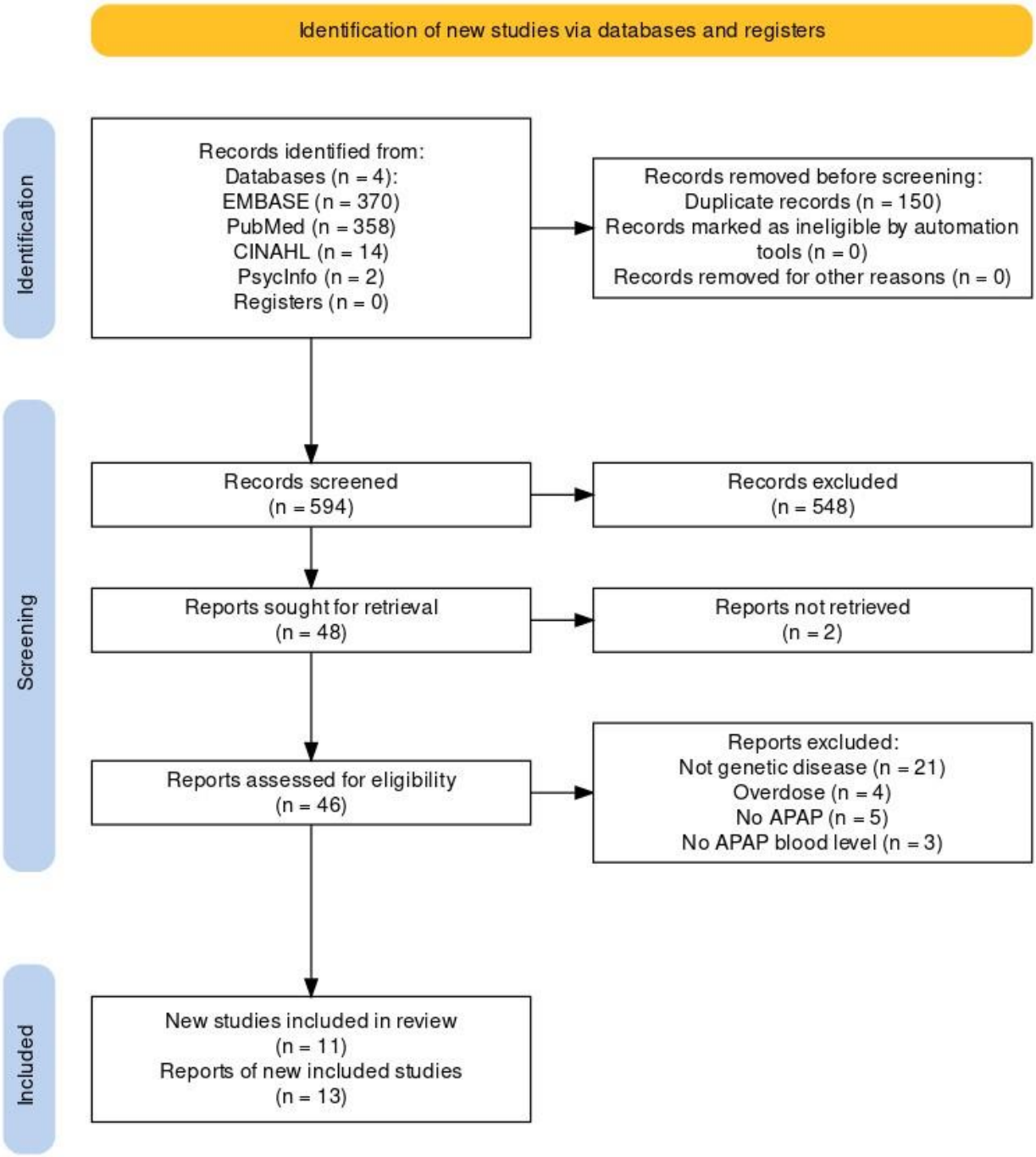
[a]Imputed APAP plasma level; median (Q1, Q3)before imputation: 273.28 (140.55, 523.32).
[b]Imputed ALT; median (Q1, Q3)before imputation: 52.50 (17.06, 87.55).
[c]Imputed ALT Times; median (Q1, Q3)before imputation: 52.53 (30.96, 147.27).
Reference APAP plasmalevel: 66 to 132 µmol/L (10 – 20 µg/mL).[32]
Reference ALT (male): 0.48 – 0.55 µkat/L (29 – 33 U/L); ALT (female): 0.32 – 0.42 µkat/L (19 – 25 U/L); AST: 0.17 – 0.57 µkat/L (10 – 34 U/L).[1]
ALT, alanine aminotransferase; APAP, paracetamol; AST, aspartate aminotransferase; D, died; NA, not available; NAC, n-acetylcysteine; PGT, pharmacogenomic test; R, recovered; Times, times upper limit of normal or times baseline value.

Table 4: Kendall rank correlation between the independent and dependent variables.

Independent variables (Exposures)	Dependent variables (Outcomes)					
	Onset		APAP level		ALT	
	Tau	p-value	Tau	p-value	Tau	p-value
APAP mg/kg/day	-0.3859	0.0431*	0.6672	0.0010*	0.3736	0.0412*
APAP level	-0.5492	0.0062*	-	-	0.3077	0.0716

Tau (one-tailed) strength of the association: very weak (0 – 0.19), weak (0.2 – 0.39), moderate (0.40 – 0.59), strong (0.6 – 0.79) or very strong (0.8 – 1);[36] *p-value significant at alpha 0.05.
APAP level is both an exposure (for liver injury) and an outcome (of dosage).
Earlier onset correlated with higher ALT (Tau -0.4394, p-value 0.0226).
ALT, alanine aminotransferase; APAP, paracetamol.

Figure: PRISMA flow diagram of the screening and selection process of studies.



DISCUSSION

Study design

This SR focused on case reports, which serve as invaluable resources for the scientific community to compile empirical evidence on adverse outcomes, particularly in rare conditions or situations where randomized controlled trials are either unavailable or unethical;[37]and genetic disorders are rare.[23]It is noteworthy that within the evidence hierarchy, case reports and case series are typically positioned at the bottom, just above expert opinion.[38]Though this may hold true for studies concerning efficacy, it may not be applicable forassessing adverse outcomes, where case reports can provide valuable insights.

The key issue: high APAP levels

Elevated levels of ALT and AST are not themselves pathognomonic of APAP toxicity, without corresponding APAP levels or other confirmatory evidence.[32]The most significant finding in our study was the high levels of APAP despite therapeutic dosing, and despite delay in measuring APAP levels after discontinuation. Severe liver damage occurs in 90% of patients with plasma levels of APAP greater than 300 µg/mL at 4 h or 45 µg/mL at 15 h after the ingestion of the drug.[7] These high levels of APAP point to pharmacokinetic problems, especially considering there was no overdose.

Medication error

Therapeutic administration of APAP resulted in harm: a medication error, which is defined as a failure in the treatment process that leads to, or has the potential to lead to, harm to the patient. Various types of errors can happen, including irrational prescribing, inappropriate prescribing, overprescribing and underprescribing.[39] Medication errors represent one of the most prevalent preventable causes of undesired adverse events in medication practice, contributing significantly to patient harm and constituting a significant public health challenge.[40]

Liver injury from APAP

Determinants, or risk factors, are characteristics of an individual or exposure that are causally related to changes in the risk of an outcome.[41]Liver damage from APAP can manifest under various circumstances, including overdose (the most critical factor), reduced capacity for glucuronidation or sulfation, excessive cytochrome P450 (CYP) activity, glutathione (GSH) deficiency or depletion, and delayed NAC therapy. Aronson has proposed a mechanistic classification of ADR[42] known as EIDOS classification, that considers the five dimensions of the ADR, complementing the previously used DoTs classification.[43] Identifying these risk factors serves as a crucial warning sign for healthcare professionals, enabling them to take appropriate action to mitigate the risk of APAP-induced liver damage and improve patient outcomes.

APAP dosage

Thedose of APAPrecommended by the FDA[7] and the BNF[9]was not exceeded in the cases under study. However, there was a relative overdose scenario, given the high serum levels observed. Although unlikely, the possibility of patients being exposed to an undocumented APAP overdose cannot be entirely ruled out. All cases, except for two, received well-documented doses in the hospital setting. Case 2 received APAP at home, while case 8 received APAP in prison. Case 8 was exclusively breastfed while mother was in prison. His mother reported taking APAP for toothache, raising the possibility that hemay havereceived additional APAPthrough breast milk.[17]

Route of administration and bioavailability of APAP

A drug administered orally undergoes the first-pass effect, where less than the full administered dose reaches the systemic circulation. This is because the drug is metabolizedin the liver before it enters the general circulation. Approximately 50% of the drug absorbed from the rectum bypasses the liver, reducing hepatic first-pass metabolism.[7] When metabolism in liver is impaired, the bioavailability of the drug increases. Factors limiting absorption are circumvented by intravenous injection of drugs because bioavailability is complete, and distribution is rapid. Thus the potential for higher and faster rise in plasma levels is highest for intravenous route, followed by rectal and oral.[7]

Volume of distribution (V_d) of APAP

V_d relates the amount of drug in the body to its concentration in the blood or plasma.[7] V_d can vary according to a patient's age, gender, body composition, and the presence of disease. APAP is relatively water-soluble and extensively distributed throughout the body, except for fat and cerebrospinal fluid.[7,44] Patients with neuromuscular disorders (NMD) and those who are malnourished typically exhibit reduced muscle mass.[45] Administering doses of APAP based on total body weight can result in a lower V_d due to the limited available muscle mass for drug distribution, leading to higher plasma levels. This can have important clinical implications, as it may necessitate adjustments in drug dosing to achieve desired therapeutic effects while minimizing the risk of ADR.

Metabolism of APAP

APAP undergoes Phase I and II metabolism in the liver.[46,47] In therapeutic doses, more than 90% of APAP is metabolized,primarily to non-toxic glucuronide (~60%) and sulphate (~35%) conjugates by UDP-glucuronosyl transferases (UGT) and sulfotransferase (SULT) enzymes, respectively.[7,47]Approximately 2% of APAP is excreted unchanged in the urine. The remaining portion undergoes oxidation by hepatic CYPmixed-function oxidase enzymes, including CYP1A2, CYP2A6, CYP2D6, CYP2E1, and CYP3A4, with CYP2E1 being the predominant enzyme involved.[48,49] This oxidative pathway generates a highly reactive and hepatotoxic intermediate known as N-acetyl-p-benzoquinoneimine (NAPQI).[48,50]The formation of NAPQI is a critical step in APAP-induced hepatotoxicity. Strategies aimed at minimizing NAPQI formation or enhancing its detoxification represent important therapeutic approaches for preventing or mitigating APAP-induced liver injury.

Adequate doses of APAP produce minimal amounts of NAPQI, which is rapidly conjugated with hepatic GSH to form non-toxic compounds.[7,47,51] Conditions associated with CYP induction, such as chronic alcohol consumption or certain drugs, as well as GSH depletion due to fasting ormalnutrition, increase the risk of hepatic injury with APAP.[7]In contrast, inhibition of CYP enzymes reducesthe formation of NAPQI, thereby decreasing the risk of hepatic injury.[52,53]

In the case of an APAP overdose, the glucuronidation and sulfation pathways become saturated, diverting more APAP (up to 50%) to the CYP pathway, where it is metabolized into large amounts of NAPQI.[54]This excess production of NAPQI overwhelms the hepatic stores of GSH, leading to depletion of GSH and

contributing significantly to the toxic effects of overdose.[7] When hepatic GSH stores are depleted by approximately 70%, NAPQI inflicts liver injury.[55]

Polymorphism in metabolism of APAP

Both Phase I and Phase II enzymes involved in APAP metabolism exhibit genetic polymorphism,[56–58]as evidenced by studies in humans and animals. Genetic polymorphism in multiple genes affecting APAP metabolism can lead to APAP accumulation due to the prominent role of these pathways in APAP metabolism.[47,59] Patients with genetic disorders may have polymorphisms in APAP metabolizing enzymes, such as UGT1A, SULT1A1 and SULT1A3.[59] Pharmacogenomic testing in case 11 indicated decreased UGT2B15 activity, and increased CYP1A2 activity,[20]the dual impact leading to the formation of more NAPQI. PharmaGKB lists several studies on genetic variants affecting APAP metabolism and adverse clinical outcomes.[59] Thus, the scenario observed in this study resembled an overdose, with impaired conjugation diverting excess APAP for oxidation,resulting inincreased NAPQI formation, utilization and depletion of GSH,ultimately leading to liver injury.

Other genetic factors

Genetic diseases, such as muscular dystrophies may predispose individuals to APAP toxicity. Carnitine deficiency (cases 6 and 8) is also linked with increased susceptibility to APAP toxicity. Carnitine has a hepatoprotective effect and potentiates the effect of NAC. When carnitine levels are deficient, APAP toxicity is heightened.[60–62] Carnitine deficiency impairs the transport of light chain fatty acids to the mitochondria matrix for oxidation, leading to hepatic steatosis and dysfunction of intermediary metabolic pathways, including the Krebs cycle, amino acid metabolism, ammonia detoxification, and beta-oxidation of fatty acids.[63] Consequently, individuals with these conditions are more vulnerable to DILI.

Age and body weight

Dosing recommendations for APAP often rely on extrapolation of pharmacokinetic data from adults, but significant differences exist in APAP pharmacokinetics across different paediatric age groups.[7] For example, APAP absorption rates may be higher in children, especially when utilizing syrup formulations,[64] and systemic bioavailability of rectal APAP formulations is greater in neonates and preterm babies compared to older patients. Additionally, APAP clearance is reduced in neonates due to their immature glucuronide conjugation system, with sulfation being the principal route of biotransformation at this age.[7] Children also have less capacity for glucuronidation of the drug compared to adults. Consequently, dosing intervals for APAP in paediatric patients may need to be extended (e.g., 8-12 hours) or daily doses reduced to prevent accumulation and liver toxicity.[7] Furthermore, infants who are breastfed may be at risk of undocumented exposure to drugs the mother may be taking.

Body weight and composition play crucial roles in determining drug dosing and plasma levels. Administering the recommended daily dose of 4g[7,9] of APAP to an underweight adult can result in higher plasma levels of the drug. Even when doses are calculated based on body weight, individuals with low muscle mass may exhibit a lower V_d of APAP, leading to higher plasma concentrations of the drug. NMD is associated with muscle wasting and low muscle mass.[45] This highlights the importance of considering not only body weight but also muscle mass and body composition when determining appropriate drug dosing regimens. Higher plasma levels of APAP in individuals with altered body composition may have clinical implications, including an increased risk of adverse effects or toxicity.

GSH deficiency

Patients with genetic disorders may exhibit GSH deficiency for various reasons, as observed in case 2 where deficient GSH synthetase led to GSH deficiency. Additionally, individuals with NMD often have low muscle mass, which may affect GSH synthesis and stores in the liver. While there is a misconception that muscle GSH protects the liver,[14,19,21] skeletal muscle plays a crucial role in glutamine synthesis, which is necessary for GSH synthesis in the liver.[65] Furthermore, malnutrition, critical illness, and concomitant medications can all contribute to GSH deficiency.[66,67] Patients with NMD, particularly those facing swallowing difficulties (case 12), may be at increased risk of malnutrition, which reduces UGT activity and GSH synthesis. Moreover, patients with infections and critical illness (cases 3, 4, 6, and 10), are prone to reduced GSH levels, rendering hepatocytes highly susceptible to oxidative stress and apoptosis.[7,68]

APAP-cysteine adducts

Serum APAP-cysteine adducts serve as valuable biomarkers for early detection and confirmation of APAP-induced liver toxicity. These adducts have been detected as early as one to two hours after commencing APAP treatment and are specific for APAP toxicity.[3,47,51,69] In patients receiving therapeutic APAP doses, adducts may either be undetectable or present at very low levels.[3,47,51,69] However, in cases where adducts are detected, such as cases 5, 6, and 7, they correlate with elevated liver enzyme levels and serve to confirm APAP-induced liver injury. Cases 5 and 6 received amoxicillin-clavulanate concurrently, and while clavulanate has been linked to drug-induced liver injury (DILI),[9] the detection of APAP-cysteine adducts in these cases confirms that the liver injury was primarily due to APAP. Serum APAP-cysteine adducts manifest early,

correlate with APAP dosage and liver enzyme levels, and can even be detected long after APAP cessation.[3,47,51,69] This makes them a valuable surrogate biomarker for predicting and confirming APAP-induced liver injury.

Concomitant drugs

Some patients were exposed to concomitant drugs, some of which posed a risk of causing liver injury. For example, case 4 was on long-term carbamazepine for epilepsy, which presents two significant interactions with APAP: both drugs can cause liver injury, and carbamazepine, by inducing CYP enzymes, may lead to increased NAPQI formation. Similarly, cases 5 and 6 received amoxicillin-clavulanate, which has been associated with DILI. Additionally, general anaesthetic agents can rarely cause liver injury.[29] While we cannot entirely dismiss the potential role of concomitant drugs in contributing to liver injury, it is crucial to emphasise that patients exhibited high serum APAP levels following therapeutic doses. The causal association between liver injury and APAP appears probable, while the association with concomitant drugs remains possible. Therefore, comprehensive evaluation and monitoring are essential in patients receiving APAP therapy, particularly those with underlying medical conditions or predisposing factors for liver injury.

Other factors

Elevations of ALT and AST are not specific to APAP toxicity and can be observed in various other conditions, including viral hepatitis, hypoxia, obstructive sleep apnoea, heat stroke, anorexia nervosa, and Epstein-Barr virus infection. Most of these were ruled out. The authors of the articles considered various factors, such as malnutrition, dehydration, hypotension, chronic hypoxia, metabolic stress of surgery, and critical illness, as possible contributors to DILI.[68] However, few considered the possible role of genetic factors. It is important to recognize that the reported cases of DILI may have been a combined outcome of both environmental factors and genetic predispositions. Further research is needed to elucidate the specific genetic factors involved in DILI and their interactions with environmental factors.

Onset and recovery

The time to onset, course of reaction, and time to resolution are crucial data points required to establish a compatible temporal relationship with the suspected causative agent in DILI. The time to onset of DILI is typically measured from the first day the suspected agent was taken to the day of onset of symptoms, jaundice, or laboratory test abnormalities, whichever occurs first.[1,70] This timeframe can vary considerably, with a large proportion of patients experiencing DILI within the first 6 months of therapy.[71] In our study, the onset of DILI was acute.

However, determining the time to recover from APAP toxicity was challenging in most cases, because many patients were admitted to the hospital for elective surgeries or critical illnesses, and the recovery from APAP toxicity may be overshadowed by the recovery from these underlying conditions. It is important to consider the overall clinical context and potential confounding factors when assessing the time course of DILI and its relationship with the suspected causative agent.

Delay in diagnosis and treatment

APAP-induced ALF is a life-threatening condition, and the timely administration of NAC can be lifesaving. A missed diagnosis, delay in treatment, or interruption of NAC infusion can have potentially lethal consequences.[72] NAC functions by repleting GSH stores and may serve as a substitute for GSH by directly conjugating with NAPQI. Additionally, aggressive supportive care is warranted in managing APAP-induced ALF, and fulminant hepatic failure may necessitate liver transplantation.[7] However, diagnosing APAP overdose can be challenging, especially in controlled hospital environments where suspicion may be low. The plasma half-life of APAP is about 2 h;[7]timely measurement of APAP blood levels is crucial to guide management decisions, as delay in measurement can result in low levels. This can falsely lower the level of urgency and lead to delays in treatment initiation. Furthermore, APAP administration may continue despite liver injury setting in, highlighting the importance of vigilant monitoring and prompt intervention in suspected cases of APAP toxicity.

Improving prevention and management

The first step in preventing APAP toxicity is to use lower doses in high-risk patients and ensure close monitoring for early detection of liver injury, as clinical manifestations typically appear after damage has occurred.[3,14] To optimize prevention and management of APAP toxicity, early diagnosis and initiation of NAC therapy are crucial.[73] The Rumack-Matthew nomogram, developed in 1975, is a valuable tool for guiding prognosis and NAC treatment in cases of acute APAP ingestion, but it may not be useful in cases of staggered or repeated dosing.[72,74] In such instances, management is determined by the patient's presentation, emphasizing the need for clinical guidelines.[72] Fulminant hepatic failure is a serious indication for liver transplantation in severe cases of APAP toxicity.[7]

Encompassed in the idea of personalised medicine is the concept of tailoring treatments to individual patients based on their molecular and genetic characteristics.[23] The implementation of genotype-guided treatment using comprehensive pharmacogenomic panels has shown promising results in reducing the incidence of clinically relevant ADR.[75] Incorporating specific biomarkers,

particularly those capable of early detection and with greater specificity and sensitivity than traditional markers like transaminases, is crucial in this endeavour. For example, APAP-protein adducts have been identified as specific biomarkers of toxic APAP metabolite exposure. Other emerging biomarkers, such as microRNAs, also hold promise in improving early detection of drug-induced liver injury. However, despite advancements in personalised medicine and biomarker discovery, there remains a need for better treatment options, particularly for patients who present late with drug-induced liver injury. Aside from liver transplantation, effective treatments for these patients are currently lacking.[55] Addressing these challenges and further developing personalised medicine approaches will require continued research and translation of genetic findings into targeted therapies.

LIMITATIONS

Case reports inherently possess biases that can pose challenges in establishing causal relationships.[41] Common selection biases and confounding variables, such as underlying medical conditions or concomitant medications, may substantially limit the ability to attribute observed outcomes solely to APAP or other suspected causative agents.[41] Additionally, temporal associations between potential causes and effects can be difficult to discern, particularly in cases with complex medical histories or multiple contributing factors.[37]While efforts are made to account for these factors, it is challenging to entirely exclude the role of concomitant drugs and other variables in causing or exacerbating liver injury. Furthermore, missing information in case reports may impact the clarity and interpretation of data, highlighting the need for thorough documentation and reporting standards.The small number of reported cases and the rarity of genetic disorders may limit generalizability, and similar cases may go unnoticed or unreported.Overall, while case reports offer important observations, their findings must be interpreted with caution and within the context of the inherent limitations of this study design.

CONCLUSIONS

In summary, this study highlights a critical concern regarding the universal applicability of the recommended therapeutic dose of APAP. Under the influence of specific risk factors or unique clinical conditions, such as genetic predispositions or concomitant medications, the therapeutic dose of APAP can inadvertently transform into an overdose, leading to toxic levels and DILI. To counteract these medication errors and enhance patient safety, vigilance is paramount, and personalised medicine grounded in pharmacogenomics holds immense promise. It is imperative to recognize that therapeutic recommendations, particularly for special populations, must undergo revision to account for individual variability in drug metabolism and response.Raising awareness and taking proactive measures to prevent such medication errors is of paramount importance. On a more practical level, we propose that in especially vulnerable populations, vigilance, a heightened level of suspicion, and the use of lower doses with therapeutic drug monitoring should be practiced. Furthermore, whenever possible, personalised medicine guided by pharmacogenomic testing should be standard practice, ensuring that treatments are tailored to individual patients' genetic profiles and minimizing the risk of ADR.

DECLARATIONS

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ABBREVIATIONS

ADR, adverse drug reaction
ALF, acute liver failure
ALT, alanine aminotransferase
APAP, N-acetyl-p-aminophenol, paracetamol, or acetaminophen
AST, aspartate aminotransferase
BNF, British National Formulary
CYP, cytochrome P450
DILI, drug-induced liver injury
FDA, Food and Drug Administration
GSH, glutathione
LFT, liver function tests
NAPQI, N-acetyl-p-benzoquinoneimine
NMD, neuromuscular disorders
SR, systematic review
SULT, sulfotransferase
UGT, UDP-glucuronosyl transferases
V_d, volume of distribution

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