Determinants of hepatotoxicity after repeated supratherapeutic paracetamol ingestion; systematic review of reported cases

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SUMMARY

AIMS: To evaluate the role of reported daily dose, age and other risk factors, and to assess the value of quantifying serum transaminase activity and paracetamol (acetaminophen) concentration at initial assessment for identifying patients at risk of hepatotoxicity following repeated supratherapeutic paracetamol ingestion (RSPI).

METHODS: Systematic literature review with collation and analysis of individual level data from reported cases of RSPI associated with liver damage.

RESULTS: In 199 cases meeting the selection criteria, severe liver damage (ALT/AST ≥1000 IU/L, liver failure or death) was reported in 186 (93%) cases including 77/78 (99%) children aged ≤6 years. Liver failure occurred in 127 (64%) cases; of these 49 (39%) died. Maximum ingested daily paracetamol doses were above UK recommendations in 143 (72%) patients. US-Australasian thresholds for repeated supratherapeutic ingestions requiring intervention were not met in 71 (36%) cases, of these 35 (49%) developed liver failure and 10 (14%) died. No cases developing liver damage had paracetamol concentration <20mg/L and a normal ALT/AST on initial presentation or when RSPI was first suspected, but these values were only both available for 79 (40%) cases.

CONCLUSIONS: Severe liver damage is reported after RSPI in adults and children, sometimes involving reported doses below current thresholds for intervention. Paracetamol concentrations <20mg/L with normal serum ALT/AST activity on initial assessment suggests a low risk of subsequent liver damage. These findings are, however, limited by low patient numbers, publication bias and the accuracy of the histories in reported cases.

What is known about this subject:

Paracetamol (acetaminophen) is widely used internationally for analgesia and in the management of fever, and it is the most frequently used over the counter medication in preschool children.

Repeated supratherapeutic paracetamol ingestion (RSPI) can cause liver damage, but there are international differences in guidance about management, including the need for assessment in hospital and appropriate use of N-acetylcysteine under these circumstances.

What this study adds:

Severe liver damage is reported after RSPI in adults and children when reported doses are below thresholds for intervention as specified in international guidelines and sometimes below UK age-specific recommended daily doses. Considering the frequency of RSPI, however, absolute risks appear extremely small.

Risk of subsequent liver damage appears very low if at initial assessment, the blood paracetamol concentration is <20mg/L and the serum ALT or AST activity is normal, although further data are needed to quantify this risk accurately.

List of Abbreviations

RSPI – Repeated Supratherapeutic Paracetamol Ingestion

ALT - Alanine Aminotransferases

AST – Aspartate Aminotransferases

RDD – Recommended Daily Dose

NAC – N-acetylcysteine

Introduction

Paracetamol (acetaminophen) is widely used internationally for analgesia and in the management of fever. More than 4 in 5 mothers in the United Kingdom use paracetamol in children under 6 months [1], and it is the most frequently used over the counter medication in preschool children in the USA [2]. In the United Kingdom (UK), recommended daily doses (RDD) range from 60 mg/kg in infants to 4g in adults, although there are international differences.

Adverse effects are unusual when paracetamol is used within the RDD [3,4], but dose-related hepatotoxicity is well recognised after overdose [5-7] and this includes repeated supratherapeutic paracetamol ingestion (RSPI) [8-10]. Recommended doses may be exceeded because of misunderstanding of dosing instructions, inadvertent combination of more than one paracetamol-containing preparation or continuing pain.

Concern about RSPI and risk of subsequent toxicity is a common reason for presentation to health services. In the UK, for example, the National Poisons Information Service reported more than 4,000 telephone enquiries from health professionals concerned about patients with accidental or therapeutic paracetamol overdoses [11] and many more would have been handled by reference to the NPIS on-line database TOXBASE [12]. In the United States, poisons centres reported more than 20,000 telephone enquiries involving children less than 5 years of age relating to paracetamol exposure alone [13].

In patients with acute overdose, there is a substantial evidence base for assessing risk by relating plasma paracetamol concentration to the time since ingestion using a nomogram, with

those identified to be at risk treated with the antidote N-acetylcysteine [14-17]. This approach, however, cannot be used for assessing RSPI, where there is a lack of evidence to guide management resulting in uncertainty and international variation in recommended management [12,18,19]. Current management guidelines [12,18,19] depend heavily on reported ingested dose for risk stratification, but risks of toxicity in relation to dose and duration of exposure are not well characterised. Furthermore, hepatotoxicity has occasionally been reported in cases where recommended therapeutic paracetamol doses had apparently been used [20-22]. Although such cases are rare, this indicates that there may be no lower dose threshold associated with zero risk. Some international guidelines also recommend measurement of paracetamol concentrations and hepatic transaminases in those with ingestions greater than specified limits; if neither are elevated, treatment with N-acetylcysteine is not recommended [18,19]. While this approach is attractive, evidence of its effectiveness in excluding patients at risk is limited.

We therefore carried out a systematic review of published cases of RSPI. The specific aims were to examine the role of the daily dose and the contribution of other factors such as age and other potential risk factors for paracetamol hepatotoxicity. We also sought to evaluate the value of measuring serum paracetamol concentrations and alanine or aspartate transaminases (ALT or AST) activities at initial presentation in predicting risk of subsequent liver damage, to inform appropriate management guidance of this very common clinical problem.

Methods

A systematic search was undertaken of OVID Medline and EMBASE databases from 1946 and 1974 respectively to September 2015 to identify case reports of non-intentional repeated

supratherapeutic ingestions of paracetamol. The full list of search terms is provided (supplement 1 online). References from retrieved articles, in addition to personal libraries, were also perused for further relevant articles.

The criteria for the selection of relevant articles included the availability of either a full text or abstract with appropriate individual patient level data including specification of paracetamol use with therapeutic intent, reported daily ingested dose of paracetamol and liver outcome either from author statement or demonstrated by results of blood tests. Data were abstracted from relevant studies by a single researcher using a structured electronic data collection form. In the case of children, total daily ingestion per kilogram body weight was calculated using the reported body weight or an estimated weight using the 50th centile of either the Royal College of Paediatrics and Child Health's UK Growth Charts for boys and girls [23,24] in reported cases from the UK or the WHO Child Growth Standards 2006 for all other reports [25]. Case reports involving intentional and/or acute overdoses of paracetamol and reports of RSPI with normal liver outcomes or tests were excluded.

Cases were classified based on dose of paracetamol ingested as (a) <75, 75-149 or ≥150 mg/kg/day, (b) whether above or below the thresholds specified in the US - Australasian guidance as being associated with hepatic damage (for example >200 mg/kg or 10 g per 24 hours in an adult or >150mg/kg per 24 hours over 48 hours in a child) [18,19] and (c) whether the ingested dose was above the UK recommended daily dosage for that individual. The effect on liver outcomes was also assessed for delay in diagnosis beyond initial presentation and assessment, treatment with NAC and risk factors for paracetamol induced liver damage (including malnutrition, starvation, use of liver enzyme inducing drugs and chronic excessive

alcohol use). Clinical characteristics were compared among the age groups <1, 1-6, 6-12 and >12 years. Severity of liver damage or outcome was graded as hepatic injury (peak ALT / AST: 2x upper limit of normal (ULN) to 999 IU/L), hepatotoxicity (peak ALT or AST: ≥1000 IU/L), hepatic failure (as defined by authors or based on clinical, biochemical and coagulation parameters) or death from liver failure. The degree of liver damage was considered to be 'severe' for those with hepatotoxicity, liver failure or death from liver failure.

Data from individual cases were collated and analysed using IBM SPSS Statistics version 22 (New York, USA). Results have been summarised using descriptive analyses for continuous variables and frequency counts with proportions for categorical data. Associations between categorised liver outcomes and potential independent risk factors were evaluated using chi square inference analysis.

Results:

Search terms generated a total of 1686 publications, and after application of the exclusion criteria including the exclusion of 7 cases with normal liver outcomes, 199 individual cases from 92 publications met the selection criteria (Figure 1). These were obtained from 61 single case articles, 17 articles with 2 cases each and 14 articles with between 3 and 22 cases each. Females and individuals >12 years old made up 53% and 56% of all cases respectively. There were significant differences across age groups for reported ingested doses, prevalence of risk factors and treatment with NAC (Table 1). A maximum reported 24-hour dose lower than the RDD was reported in 56 (28%) cases and this was significantly more common in those over 12 years than those under 6 years of age (43% [n=48] vs 6% [n=5], p value <0.001). Across all age groups, a reported dose below current US and Australasian criteria for intervention was

reported in 71 (36%) cases, without statistically significant differences between age groups (Table 1).

Serum paracetamol concentrations were reported for 123 (62%) cases and the time of sampling relative to the last ingested dose was available for 79 (64%) of these. Although not valid for use with chronic or repeated paracetamol overdose, these timed paracetamol concentrations were usually above the nomogram thresholds used for acute overdose in the UK (n=61, 77%) and also the higher thresholds used in the USA and Australasia (n=58, 73%). Of the 20 patients with available timed paracetamol concentration who died, 18 had paracetamol concentrations above both the UK and US/Australian treatment lines. Similarly, of the 77 patients with timed paracetamol concentrations who developed severe liver damage, paracetamol concentrations were above the current UK threshold in 60 (78%) cases and the higher US-Australian threshold in 57 (74%) cases (Figure 2). This high frequency of elevated paracetamol concentrations was documented in spite of the modest daily doses commonly reported.

Paired paracetamol concentration and ALT / AST activity from samples collected during initial presentation / assessment were available in 24 of the 199 cases. Of these 24 cases, paracetamol concentrations were elevated (>20 mg/L) in 22 cases, ALT/AST activities (> ULN) were elevated in 23 cases, both paracetamol concentration and ALT/AST activity were elevated in 21 cases and no case had normal paracetamol concentration and ALT/AST activity. Presentation and peak serum ALT/ AST activities were significantly higher in those who ingested paracetamol doses above 150mg/kg/day, RDD and US-Australasian treatment thresholds reflecting the dose associated risk to the development of liver damage (Table 2).

The relationship between paracetamol concentration, admission or initial ALT / AST activities and liver outcome is illustrated in Figure 3.

Severe liver damage was reported in 186 (93%) cases including 77/78 (99%) children ≤6 years. Liver failure occurred in 64% of all cases and resulted in an overall mortality of 39%. Of the 71 (36%) reported cases that did not meet the US - Australasia criteria for RSPI, 35 (48%) developed liver failure and 10 died. The proportion of cases with severe liver damage was high irrespective of the reported dose, but was significantly higher in those with risk factors and in those with larger reported paracetamol doses, expressed in mg/kg/day, in relation to US-Australasia criteria or maximum RDD (Table 3).

The use of NAC was not different across the various ingested doses of paracetamol but was more common in those with more severe liver outcomes (Table 4).

Discussion

This systematic review shows that repeated supratherapeutic paracetamol ingestions associated with liver damage have been reported across all age and sex groups but most commonly in those >12 years old. In most reported cases, the diagnosis of RSPI was delayed following hospital presentation; paracetamol concentrations and liver function tests taken during initial assessment were reported in only a minority of cases. The prevalence of severe liver damage including death from liver failure was high in this series of published cases, especially in children ≤6 years old. It should be noted, however, that this contrasts with the very low overall incidence of fatal paracetamol poisoning in children in other published evidence; for example,

there were only 3 deaths reported in children ≤5 years from over 120,000 cases of paracetamol exposures reported to poison centres in USA between 2010 and 2014 [13,26-29].

Although there is evidence for a relationship between reported daily dose and risk of severe outcomes after RSPI, arbitrary thresholds based on weight-corrected ingested daily doses of paracetamol appear to be of limited value for risk stratification. There were patients who developed liver damage when their reported paracetamol intake was below US/Australasian criteria for intervention, including some ingesting less than the RDD. However, the high prevalence of high paracetamol concentrations measured in blood suggests that in some of these reported cases, ingested doses were substantially underestimated.

The association of liver damage with both elevated ALT / AST activity and paracetamol concentration ≥20mg/L on initial presentation, suggest that cases with normal ALT / AST and paracetamol concentration <20mg/L at initial presentation following RSPI are at very low risk of developing liver damage. This is consistent with the results of two previous studies in which patients presenting with RSPI did not develop severe hepatotoxicity if they presented with normal liver transaminases [30,31]. We acknowledge that in our systematic review both of these biochemical variables were only reported on initial presentation / assessment in a minority of reported cases and a much larger case series would be needed to accurately quantify the risk of developing liver damage in RSPI patients with low paracetamol concentration and transaminase activity at presentation. However, the lack of any cases in the published literature of severe liver damage following initially normal ALT / AST activity and a paracetamol concentration <20mg/L, even though this method of risk stratification has been used in North

America and Australasia for almost a decade, is strong evidence that this method can be used to identify patients who do not need further investigations or treatment.

In this review, the use of NAC was reported in 67 (34%) cases overall; a larger number would have been treated if current UK or US/Australasian recommendations had been used [12,19], but many of these cases were reported before such guidance was published. Patients in this series who were treated with NAC often had more severe liver outcomes than those not treated; this does not mean that NAC is ineffective or even harmful as this is not a randomised comparison. It is more likely that this reflects the preferential use of NAC in sicker patients with deteriorating liver function in the pre-guidance era.

Interpretation of this systematic review of case reports is limited by three major factors. Firstly, reporting bias is inevitable and likely to be substantial; cases without liver damage or dysfunction are unlikely to be published, while reporting and publication are much more likely in those where low ingested doses are reported or where liver outcomes are severe. It is less likely that cases who did not develop liver damage after ingesting a low dose, or those developing liver damage after massive doses, will be published and the former were not included in this review. Secondly, we do not know the overall numbers of patients presenting to hospitals with RSPI, or within particular dose ranges (e.g. <75, 75-150, >150 mg/kg/24h etc.) so we cannot accurately estimate the proportion of cases that develop liver damage at these doses. Minor therapeutic overdose is probably more common than major supratherapeutic paracetamol ingestions. Ingested doses may also vary with age, country and prevalence of other associated risks relevant to the development of liver damage. Thirdly, we are dependent on the accuracy of the history, especially ingested dose and duration, as reported by the patients and

their relations. The very high paracetamol concentrations seen in some cases suggest that these are sometimes substantial underestimates of the doses that are involved. It is also a limitation that abstraction in this study was done by a single observer, as there were inadequate resources available for double abstraction to be performed.

Conclusion

In conclusion, there are many reported cases of supratherapeutic paracetamol ingestion associated with severe hepatotoxicity or death, especially in younger children. Thresholds based on weight-adjusted daily paracetamol doses may be of limited value in risk stratification as cases with severe liver outcomes are reported after doses apparently below currently recommended thresholds. A low or undetectable paracetamol concentration associated with normal transaminases activity on initial assessment of RSPI appears to indicate a low probability of subsequent severe liver damage, but numbers of cases studied are limited and further data should be collected to quantify this risk more accurately.

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 organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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Legends to Figures

Figure 1: Flow diagram for publication review and article selection.

Figure 2: Liver outcome (hepatic injury ▲, hepatotoxicity +, liver failure ◊, death ■) relative to timed serum paracetamol concentrations with illustration of the UK (▬) and US (- -) treatment lines for acute paracetamol ingestion.

Figure 3: Liver outcome (hepatic injury ▲, hepatotoxicity +, liver failure ◊ and death ■) relative to serum paracetamol concentration and initial ALT or AST activity. AST – Aspartate aminotransferase; ALT – Alanine aminotransferase.