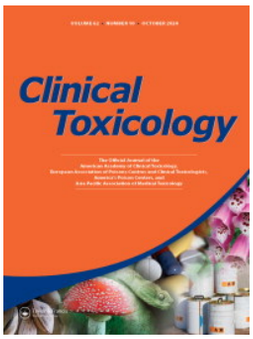

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POISON CENTRE RESEARCH

The impact of updated national guidelines for managing unintentional paediatric liquid paracetamol exposures: a retrospective poisons centre study

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ABSTRACT

Introduction: In 2015, Australia and New Zealand treatment guidelines recommended a 2 h paracetamol serum concentration for risk assessment of unintentional paracetamol liquid exposures. We assess our experience with this approach.

Methods: Retrospective case review of children <6 years-old with liquid paracetamol overdoses referred to a regional poisons information centre January 2017 to August 2022. We extracted data on the exposure and management from the poisons information centre and hospital medical records. We identified additional cases with two paracetamol concentrations obtained from September 2022 to June 2024.

Results: Of 437 paediatric poisonings, 271 were eligible for inclusion. The median age was 24 months, the median time to presentation was 120 min, and paracetamol was the sole ingestant in 92% of cases. Blood testing was recommended in 131 patients (48.3%), occurring at 2 h post-ingestion in 62 patients (47.3%). Testing at a later time was mostly due to delayed presentation, including to hospitals unable to measure paracetamol concentrations. Eighteen patients (16.7%) had repeat blood testing, and five additional cases were identified in the subsequent period. Overall, the concentration decreased in 19 patients (83%), but in three patients it increased, from 73 mg/L to 81 mg/L (0.49–0.54 mmol/L), from 154 mg/L to 179 mg/L (1.03–1.19 mmol/L), and from 56 mg/L to 115 mg/L (0.37–0.77 mmol/L. Symptomatic patients were more likely to receive a second blood test or acetylcysteine while awaiting investigations. Of 19 patients administered acetylcysteine, it was discontinued in five due to low paracetamol serum concentrations. All patients recovered.

Discussion: Guidelines were followed in >90% of patients and this testing regimen shortened length of stay. Based on these data, Australian treatment guidelines now recommend repeat testing for 2 h paracetamol serum concentrations >100 mg/L (0.67 mmol/L).

Conclusion: A paracetamol serum concentration between 2 h and 4 h post-ingestion in children <6 years-old with unintentional poisonings of paracetamol liquid can facilitate medical discharge.

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Acetaminophen; acute; guidelines; paracetamol; poisoning; risk assessment

Introduction

Paracetamol (acetaminophen) is a widely used nonprescription analgesic that is a common cause of paediatric poisoning in Australia [1] and elsewhere, such as in the United States [2]. Paediatric paracetamol poisonings are usually unintentional and with a liquid formulation. Historically, in Australia and New Zealand they were managed similarly to deliberate self-poisoning with paracetamol tablets [3]. In this context, when measuring the paracetamol serum concentration was indicated, this was conducted at least 4 h post-ingestion [3].

The lower risk of adverse outcomes from unintentional paediatric paracetamol poisoning, and differences in paracetamol pharmacokinetics between solid and liquid oral formulations prompted a review of this testing regimen in Australia and New Zealand. A study informing this review was a population pharmacokinetic study that concluded that 95% of children ingesting a liquid formulation would obtain a maximum paracetamol serum concentration within 2 h post-ingestion [4]. Therefore, in 2015 the updated Australian and New Zealand paracetamol treatment guidelines [5] recommended that the paracetamol serum concentration should be measured at 2 h (to 4 h) post-ingestion in children <6 years-old with unintentional at-risk exposures. If the concentration exceeds 150 mg/L (1 mmol/L) then the concentration is rechecked at 4 h post-ingestion and management follows standard recommendations, including treatment with intravenous acetylcysteine if the 4 h concentration exceeds 150 mg/L (1 mmol/L).

Anticipated benefits of this new protocol were earlier medical discharge in a patient population who uncommonly require acetylcysteine treatment [5]. However, potential concerns included increased blood testing in this paediatric

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cohort, for example testing occurring at 2 h and 4 h post-ingestion due to unfamiliarity or uncertainty with the guidelines, or other reasons. Additional blood testing may increase distress to the child or others, without facilitating an earlier discharge. The Australian and New Zealand guidelines were updated in 2020 and these recommendations were unchanged [6].

We evaluated our experience with this change in protocol for managing paediatric paracetamol liquid exposures. In doing so, we hypothesised that the new guidelines facilitated early discharge without increasing blood tests. We assessed compliance with the updated guidelines, on the basis of the management plan provided by the New South Wales Poisons Information Centre and that enacted by the hospital. In those patients receiving two blood tests, we assessed whether the paracetamol serum concentration-time profile decreased after the 2 h time-point, as described in the pharmacokinetic publication [4] that informed the change in guidelines. Finally, we considered the impact of this research on the current Australia and New Zealand guidelines.

Materials and methods

Study design and setting

We performed a retrospective case review of paediatric patients <6 years-old with liquid paracetamol overdoses who were referred to the New South Wales Poisons Information Centre between 1st January 2017 and 31st August 2022.

The New South Wales Poisons Information Centre managed nearly 120,000 incoming calls/year, which was approximately half of the calls answered by Australian poisons information centres each year. Australian poisons information centres answered calls from both the public and medical professionals. Calls were answered by specialists in poisons information (SPIs) who provide advice regarding poison-related exposures. The SPIs are mostly clinical pharmacists, or science graduates with a pharmacology major, and all SPIs receive specialist training in poisons information and clinical toxicology. For each call, information was obtained on the demographics of the person exposed, circumstances of the exposure, substances and amount, and poisoning symptoms at the time of the call. These and other predefined data fields in the New South Wales Poisons Information Centre database are routinely completed. The SPIs used this information to perform a risk assessment and provide individualised management recommendations. Complex, severe or unusual cases were referred to a medically trained clinical toxicologist.

Patient selection and data collection

We identified eligible cases by searching the New South Wales Poisons Information Centre clinical database for calls from healthcare workers in hospitals that fulfilled the inclusion and exclusion criteria. Inclusion criteria were children <6 years-old with unintentional poisoning with paracetamol liquid formulations in hospital. Exclusion criteria included exposures to non-liquid paracetamol formulations, or when there were insufficient data to evaluate management and outcomes, for example incomplete identifiers in the New South Wales Poisons Information Centre database, which precluded reviewing patient progress in the hospital electronic medical record.

We extracted clinical data from the electronic medical record of both the poisons information centre and referring hospital into a custom-built spreadsheet (Supplementary material). This data extraction spreadsheet was designed by two authors who are both clinicians experienced in the subject area and the databases and medical records that the data were to be extracted from. The data fields included in the data extraction spreadsheet reflect questions that are routinely asked during the assessment of unintentional paediatric paracetamol poisoning. When data were not available, the field was left empty. The spreadsheet was tested during the training of two final year pharmacy students who performed the initial data extraction. A third abstractor (medical specialist in the field of emergency medicine and clinical toxicology) was also trained on the use of the spreadsheet and databases, and served as a double check of information extracted by the initial abstractors.

Most hospital electronic medical records in our state are directly accessible by the New South Wales Poisons Information Centre staff. In the small number of hospitals where this was not possible, the patient notes were directly requested from the medical records department of that hospital. We collected demographic information, details of the exposure, details of blood tests (including reasons for deviating from recommended testing) and the results (Supplementary material). If conflicting information was noted between the poisons information centre and hospital medical records, we accepted the more recent documentation because this generally related to new information. The estimated exposure to paracetamol liquid was recorded, and we graded the confidence in the estimated dose into three categories: high (the amount taken or given was known precisely), medium (a good estimate, but with some uncertainty), and low (very much a worst-case scenario) (Supplementary material).

We considered exposure to paracetamol 200 mg/kg or more as a single dose as the usual indication for blood testing [6], based on best estimate or worst-case scenario. Paracetamol exposures below 200 mg/kg are considered low risk and not requiring blood tests for further risk assessment [6]. The paracetamol serum concentration is used for further risk stratification and treatment with acetylcysteine. Treatments administered, including decontamination and intravenous acetylcysteine, were extracted.

Using the same methods, we performed a targeted sub-study of all unintentional paediatric paracetamol poisonings in children <6 years-old between 1 September 2022 and 30 June 2024 to identify other children in whom two paracetamol concentrations were obtained around the 2 h and 4 h post-ingestion time points.

We were required to perform a post hoc review of the methodology utilised in our study to those described in a 2014 publication [7], during the peer review of our manuscript. This is summarised in the Supplementary material.

Statistics

We expressed categorical variables as counts and percentages. Continuous data were expressed as median, interquartile range (IQR) and range. We defined a decrease or increase in paracetamol serum concentrations between subsequent time points when it changed by more than 10%. Statistics were conducted using GraphPad Prism version 9.1.1 for Windows, GraphPad Software, San Diego, CA, USA).

Ethics

This study was approved by The Sydney Children's Hospitals Network Human Research Ethics Committee (Approval number 2021/ETH00165).

Results

We received calls relating to 437 paediatric paracetamol poisonings during the study period. We excluded 166 patients, mostly due to ingestion of a non-liquid formulation ($n = 127$; 63% of excluded patients); other exclusions are shown in Figure 1. The remaining 271 (57.4%) patients were included in the analysis. All patients recovered.

Of the 271 patients included in the analysis, 121 (44.6%) were female, the median age was 24 months (IQR: 16–36 months, range 0.1–72 months). The median time to hospital presentation was 120 mins (IQR: 60–260 min, range 5 min to 10 days); this was not documented in 10 patients. In 250 patients (92%) paracetamol was the sole ingestant, with the most common coingestant being nonsteroidal anti-inflammatory drugs in five patients. The median dose ingested was 150 mg/kg body weight (IQR: 80–227 mg/kg, range 8.5–788 mg/kg; recorded in 257 patients). However, the confidence on this estimate was low for 80 (30%) of exposures, medium for 60 (22%) of exposures, and high for 131 (48%) of exposures (Figure 2).

Prior to the call to the poisons information centre, two patients received a single dose of activated charcoal; it was planned in a third child but not given on the advice of the SPI. Activated charcoal was not recommended by SPIs for any case.

Blood testing was performed in 27 patients (10% of all patients) prior to the poisons information centre call, but nine (33% of these patients) would not have required testing due to a history of low-risk exposure (less than 200 mg/kg paracetamol based on best estimate or worst-case scenario), according to the Australian and New Zealand guidelines [6]. The median and IQR paracetamol concentration at 2 h to 4 h post-ingestion for each group, relative to the confidence in the estimated dose, was 20 (IQR: 22–56) mg/L (median 0.13 mmol/L; IQR 0.15–0.37 mmol/L) for low, 35 (IQR: 20–68) mg/L (median 0.23 mmol/L; IQR 0.13 – 0.45 mmol/L) for medium and 22 (IQR: 20–55) mg/L (median 0.15 mmol/L; IQR 0.13 – 0.37 mmol/L) for high confidence (Figure 2).

From the history of exposure, 140 patients (51.7%) were assessed by the poisons information centre staff as being at low risk of toxicity (less than 200 mg/kg paracetamol based on best estimate or worst-case scenario) and it was advised that blood tests were not required. However, blood tests were obtained in 11 cases (7.9% of patients with low-risk exposures) and the reasons for doing so are outlined in Table 1. In each case, the measured paracetamol serum concentrations confirmed a low risk of toxicity, consistent with the history of exposure. The SPIs were more likely to recommend quantification of the paracetamol concentration when there was a low or medium confidence in the estimated dose of exposure (Figure 3).

A child presented to hospital 1 h post-ingestion and the advice from the poisons information centre was to wait for the 2 h paracetamol serum concentration to guide further management, even though the results were anticipated to take 2 h due to being sent to another hospital. However, the treating doctor collected the initial blood sample at 1 h and

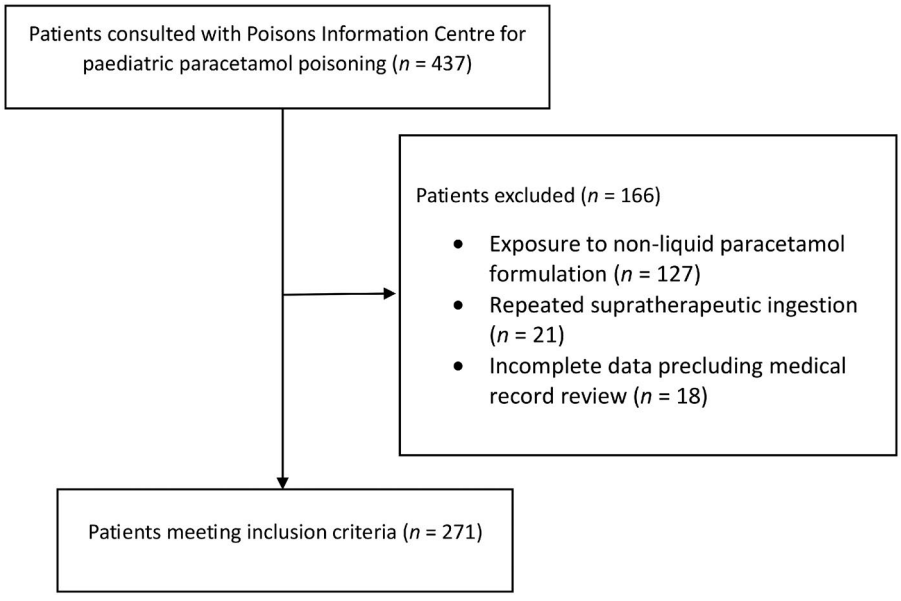

Figure 1. Recruitment flow chart.

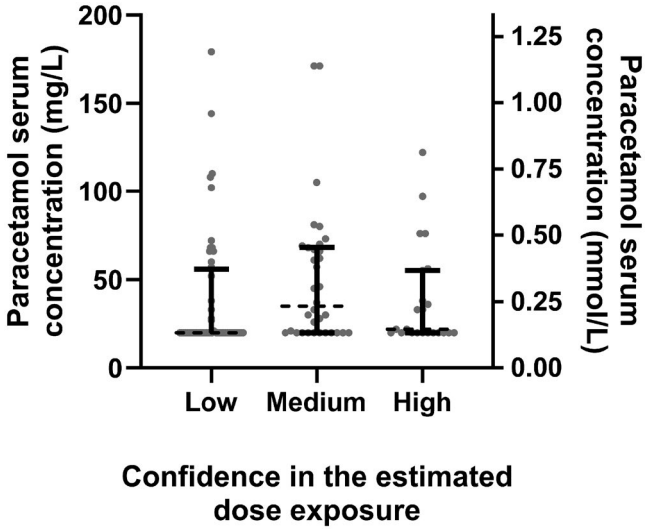

Figure 2. Paracetamol serum concentrations 2 h to 4 h post-ingestion, relative to the confidence in the estimated dose exposure*.
*Data summarised as the median (dashed line) and interquartile range (solid lines).

Table 1. Reasons for blood test in low-risk group patients.

Reason	*n*
Doctor initiated for an undocumented reason	2
Patient became symptomatic in hospital	2
Bloods taken prior to calling the poisons information centre	4
Parents request, or to reassure anxious parents	2
Deranged liver function tests on screening blood	1
Total	**11**

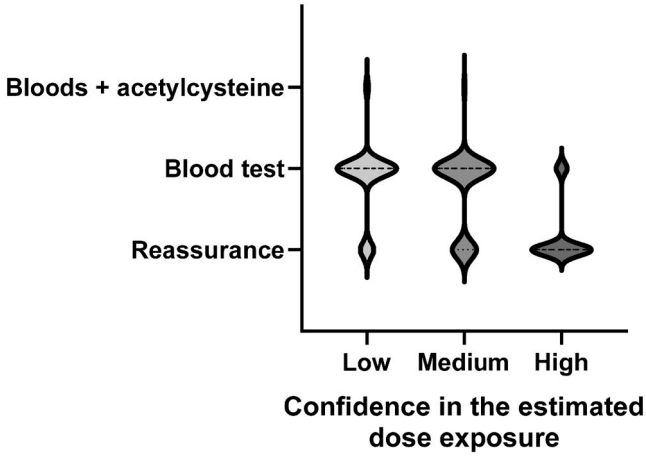

Figure 3. Violin plot showing the relationship between confidence in the estimated dose and the initial recommendations by the specialist in poisons Information*.
*One case of high confidence is excluded because the initial advice was reassurance, but the patient had already received blood tests and treatment with acetylcysteine prior to the poisons information centre being contacted.

commenced intravenous acetylcysteine out of concern for potentially high dose ingested. The paracetamol serum concentrations were 122 mg/L (0.81 mmol/L) at 1 h and 70 mg/L (0.47 mmol/L) at 4 h post-ingestion, which did not indicate that treatment was required, allowing the patient to be discharged.

Blood testing was recommended in 131 patients (48.3%) due to a potential at-risk exposure. Among these, 62 patients (47.3%) received their blood test at approximately 2 h post-ingestion as advised by poisons information centre and as per the Australia and New Zealand guidelines [6]. In the 68 patients (51.9%) who had a blood test conducted more than 2 h post-ingestion, this was mostly due to a delayed presentation to hospital in 62 patients (91% of patients with blood testing more than 2 h post-ingestion). Here, 12 patients presented to a facility without capabilities to measure paracetamol serum concentrations, 11 of whom were transferred to another facility for testing. The final case (mentioned above) remained in the hospital while blood samples were sent to another hospital for testing. In one case the treating clinician delayed testing to 4 h post-ingestion.

Table 2. Reasons for a second blood test being performed.

Reason	*n*
Initial paracetamol serum concentration >150 mg/L (1 mmol/L)	2
Doctor initiated for an undocumented reason	6
Patient symptomatic or had an abnormal alanine aminotransferase activity on initial blood testing	4
Poisons information centre advice due to uncertain time of ingestion	3
First blood test performed too early	1
Logistics with interhospital transfer	1
Miscommunication or misunderstanding of poisons information centre advice	1
Total	**18**

Repeat paracetamol serum concentration testing was performed in 18 patients (16.7%) in the main study period, mostly at 4 h post-ingestion. Reasons for repeat testing included an initial paracetamol serum concentration >150 mg/L (1 mmol/L), testing logistics, patient symptoms, or doctor-initiated for other reasons (Table 2). The subsequent sub-study identified an additional five patients in whom repeat testing occurred and the paracetamol concentrations were detectable. Here, the paracetamol concentration decreased in four patients and increased in one patient.

Figure 4 shows the paracetamol serum concentrations obtained in 141 patients; results are not shown for five patients who had testing 24 h post-ingestion, and one patient in whom the time of ingestion was not known. Figure 4 includes 23 patients with samples collected at approximately 2 h and 4 h post-ingestion, in whom the concentration decreased in 19 patients (83%) and was similar in one case. However, in two 3 year-old patients it increased, from 73 mg/L to 81 mg/L (0.49 mmol/L to 0.54 mmol/L) and from 154 mg/L to 179 mg/L (1.03 mmol/L to 1.19 mmol/L); in a 2 year-old the paracetamol concentration increased from 56 mg/L to 115 mg/L (0.37 mmol/L to 0.77 mmol/L). Overall, the number of unnecessary tests did not decrease over the duration of the study, in part due to the generally low number of tests annually, indicating that the incidence of children receiving inappropriate testing is low.

Acetylcysteine was administered to 19 patients (see Table 3 for indications), one prior to calling the poisons information centre. In this case, the poisons information centre was first contacted towards the conclusion of the acetylcysteine course seeking advice regarding cessation criteria, but on review of blood tests, acetylcysteine was not indicated. In 14 patients the full acetylcysteine course was completed, and in five patients it was ceased early once the paracetamol serum concentration confirmed a low risk of toxicity.

Three cases were referred to a clinical toxicologist for further advice. One case was for a second opinion regarding

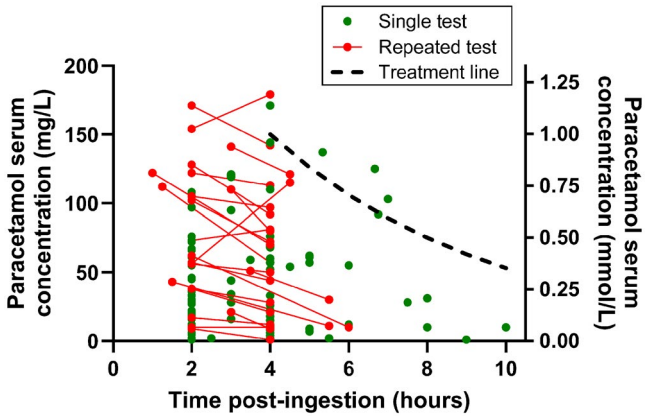

Figure 4. Paracetamol serum concentrations relative to the time since ingestion, and the treatment nomogram.

Table 3. Reasons for initiating acetylcysteine.

Reason	*n*
Potentially toxic exposure (>200 mg/kg), and delayed hospital presentation	7
Paracetamol serum concentration near or above the treatment line on the nomogram	6
Anticipated delay in obtaining blood results due to logistics with interhospital transfer	4
Potentially toxic dose (240 mg/kg) with vomiting and increasing alanine aminotransferase activity despite low toxicity paracetamol serum concentration (97 mg/L [0.65 mmol/L] at 4 h post-ingestion)	1
Potentially toxic exposure (>200 mg/kg) with vomiting and abdominal pain	1
Total	**19**

paracetamol serum concentration 125 mg/L (0.83 mmol/L) at an uncertain time of ingestion, but potentially above the treatment nomogram, so acetylcysteine was recommended. Another case was a 2-day-old neonate with a 10-fold dosing error with isolated elevated aspartate aminotransaminase activity (109 IU/L; alanine aminotransferase activity was normal at 14 IU/L) with paracetamol serum concentrations 56 mg/L (0.37 mmol/L) at 2 h post-ingestion and 50 mg/L (0.33 mmol/L) at 4 h post-ingestion, for which acetylcysteine was not recommended and the patient recovered without adverse outcomes. The third case developed hepatotoxicity which probably related to individual susceptibility and has been described elsewhere [8]. In this patient, the paracetamol serum concentration was 105 mg/L (0.70 mmol/L) at 2 h and 97 mg/L (0.65 mmol/L) at 4 h with mildly abnormal aminotransferase activities. The child remained in hospital for observation due to non-specific gastrointestinal symptoms, and due to increasing aminotransferase activities was commenced on acetylcysteine 25 h post-ingestion [8].

During our review of the hospital medical records, we did not encounter any reports of children included in this study who subsequently developed symptoms or biochemical evidence of hepatotoxicity.

Subsequent consideration of these data, particularly the increase in paracetamol serum concentrations in three patients after 2 h post-ingestion, has prompted a change in the Australian treatment guidelines, whereby the criteria for repeat testing at 4 h post-ingestion was conservatively decreased to 100 mg/L (0.67 mmol/L). Based on data from our case series, this lower threshold would prompt additional blood testing in only four patients, with concentrations of 102 mg/L to 122 mg/L (0.68 mmol/L to 0.81 mmol/L). However, two of these patients subsequently developed symptoms (both had vomiting and one also had reduced urine output) which prompted the clinicians to initiate repeat blood testing. Therefore, overall, the lowering of the criteria for repeat testing would not result in a significant increase in the number of patients undergoing additional blood testing, on the basis of these data.

Discussion

We describe the experience of a poisons information centre with new national treatment guidelines for unintentional paediatric poisoning. Of the 279 patients fulfilling our inclusion criteria, we observed that the guidelines were followed in more than 90% of patients. We observed in 23 cases with serum paracetamol concentrations taken at two different time points, that it decreased between the 2 h and 4 h samples in 83% of patients, was similar in one patient, and increased in three patients (13%). Adverse outcomes were not observed from this unexpected increase in paracetamol serum concentrations in three patients. Nevertheless, in response to this observation, national treatment guidelines have now been updated to prompt a second paracetamol serum concentration at 4 h, when the serum concentration in the 2 h sample is >100 mg/L (0.67 mmol/L), previously > 150 mg/L (1 mmol/L). Asymptomatic children who received a blood test prior to 4 h post-ingestion were cleared of significant paracetamol poisoning, facilitating an earlier discharge from hospital. Symptomatic patients were more likely to receive a second blood test or treatment with acetylcysteine while awaiting the results of blood tests. Most patients did not require acetylcysteine due to low paracetamol serum concentrations, as anticipated with unintentional paediatric exposures.

The testing protocol assessed in this study is based on a pharmacokinetic modelling study using data from 121 children aged 1 to 5 years with unintentional ingestion of paracetamol liquid who had blood tests at 4 h post-ingestion [4]. This publication describes that children aged 1 year to 5 years are at less risk of paracetamol toxicity due to their physiology. None of the children included in the pharmacokinetic study were treated with acetylcysteine because they did not reach the treatment threshold of 200 mg/L (1.33 mmol/L) used in that study [4], but it did include patients with concentrations exceeding 150 mg/L (1 mmol/L) which is the treatment threshold in the Australia and New Zealand guidelines [3]. More than 50% of children received gastrointestinal decontamination, but the model indicated no effect from activated charcoal; it could not exclude an effect if given within 60 min of exposure. It predicted that 95% of children would have a maximum paracetamol serum concentration before 2 h post-ingestion [4]. Key data informing the pharmacokinetic model were paracetamol serum concentrations following perioperative administration of therapeutic paracetamol liquid (approximately 40 mg/kg) to children undergoing a surgical procedure [9]. In this study, paracetamol concentrations were generally noted to decrease from 1 h post-ingestion, despite the absorption half-life being calculated to be 1 h [9].

It is commonplace for unintentional exposures in young children to have a low risk of significant poisoning from unintentional exposures [10–14]. Few patients were given charcoal in our study, compared to many older studies. However, the risk of a significant exposure following unintentional poisonings in children is not negligible. Of the 7% of children in this study who were initiated on acetylcysteine, the course was completed in only 5.2% of children and it was not required in all of these patients (Table 3).

We are not aware of other treatment protocols for paediatric paracetamol poisoning that recommend measuring of a paracetamol serum concentration at 2 h post-ingestion. On the basis of these data, this appears to be useful at excluding a significant poisoning in the majority of patients. In the two cases in which the paracetamol serum concentration increased, this was not to a large extent and can be accounted for by dropping the threshold for a second paracetamol concentration to 100 mg/L (0.67 mmol/L).

This research has a number of limitations. It is a retrospective study which has well known limitations, although our patients were reasonably homogenous based on age and exposures. We are unable to ascertain whether unintentional paediatric paracetamol poisonings referred to our poisons information centre differ from those that present to hospitals but are not referred to a poisons information centre. Abstractors were not blinded to the study hypothesis and while two abstractors reviewed the records of each case we did not formally assess the abstractor interrater reliability. Repeat blood testing was only performed in 23 children, and the concentration increased in three of these. In Australia, it would be extremely uncommon for potentially toxic paracetamol exposures to be managed in the community, for example by general practitioners.

Conclusion

A paracetamol serum concentration between 2 h and 4 h post-ingestion in unintentional poisonings of paracetamol liquid in children <6 years-old can facilitate medical clearance from paracetamol poisoning. These data support national guidelines that were initially based on pharmacokinetic modelling data. We observed good compliance with these guidelines.

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Disclosure statement

The authors report there are no competing interests to declare. Specifically, the authors of this research project are not authors or contributors to the Australian and New Zealand Guidelines that are being assessed.

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Data availability statement

The participants of this study did not give written consent for their data to be shared publicly, so due to the sensitive nature of the research supporting data are not available.

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