Medication errors involving intravenous paracetamol in children: experience from enquiries to the National Poisons Information Service

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ABSTRACT

Introduction Children are at higher risk of medication errors due to the complexity of drug prescribing and administration in this patient group. Intravenous (IV) paracetamol overdose differs from overdose by ingestion as there is no enteral absorptive buffering. We provide the first national UK data focusing on paediatric IV paracetamol poisoning.

Methods All telephone enquiries to the National Poisons Information Service between 2008 and 2021 regarding children less than 18 years old in the UK concerning IV paracetamol overdose were extracted from the UK Poisons Information Database (UKPID). Data were analysed using descriptive statistics.

Results Enquiries were made concerning 266 children, mostly involving children under the age of 1 year (n=145; 54.5%). Acute and staggered overdoses were the most frequent types of exposure. Common error themes included 10-fold overdose in 45 cases (16.9%) and inadvertent concomitant oral and IV dosing in 64 cases (24.1%). A high proportion of cases were asymptomatic (87.1%), with many calls regarding overdoses below the treatable dose of 60 mg/kg (41.4%). Treatment with the antidote acetylcysteine was advised in 113 cases (42.5%).

Conclusions Inadvertent IV paracetamol overdose appears to occur more frequently in young children. A significant proportion were calculation errors which were often 10-fold errors. While these errors have the potential for causing serious harm, thankfully most cases were asymptomatic. Errors with IV paracetamol might be reduced by electronic prescribing support systems, better communication regarding administration and consideration of whether other routes are more appropriate.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Children are more prone than adults to medication errors because of their dependency and inherent complexities in prescribing.
⇒ Oral paracetamol overdose is well recognised, but data regarding intravenous paracetamol poisoning in children are limited to case reports or small case series.
⇒ No published UK data exist for population-based intravenous paracetamol poisoning.

WHAT THIS STUDY ADDS

⇒ Young children appear to be at higher risk of intravenous paracetamol overdose, either from erroneous calculation/prescribing or dual dosing administration errors.
⇒ Seeking telephone advice for intravenous paracetamol overdose is infrequent while TOXBASE accesses increased throughout the study period.
⇒ Severe harm appears uncommon, but outcome data are limited.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlights the need for utilisation of pharmacovigilance data to explore intravenous paracetamol use in children and its effects.
⇒ It demonstrates the ongoing need for healthcare education to support safe prescribing and minimise harm.
⇒ Intravenous paracetamol overdoses may be reduced by the wider adoption of electronic prescribing systems and the consideration of alternative routes of paracetamol administration.

INTRODUCTION

Oral paracetamol has been widely used as an analgesic and antipyretic since the 1950s. It is a well-tolerated analgesic and safe in standard doses. Intravenous (IV) paracetamol was first introduced in the UK in 2003.[1] The IV route is only clinically indicated when the patient urgently requires its analgesic effects and is unable to take paracetamol orally or rectally.

Medication errors are common with 237 million medication errors occurring at some point in the medication process in England per year.[2] Paracetamol (both oral and IV) was the most reported substance involved in medication error enquiries identified by the National Poisons Information Service (NPIS) in their latest annual report across all their platforms.[3] The high prevalence of errors reported to the NPIS may be due to paracetamol being more frequently used proportionately than other drugs. Thus, this may innately lead to an increased potential risk from overdose and subsequent harm. Measures to mitigate these errors include electronic physician support systems which can reduce some types of error. However, given that human factors such as communication issues have an important role in healthcare, a whole systems approach is needed to solve medication errors.[4]

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Table 1 MAXPSS in cases reported to the NPIS (after 2010)

MAXPSS (n=232)			
	Examples	**Frequency (n)**	**Per cent (%)**
Unknown		5	2.2
None	No signs or symptoms	202	87.1
Minor	Rise (2–5 times the normal value) in serum transaminases	18	7.8
Moderate	Rise (5–50 times the normal value) in serum transaminases but no diagnostic biochemical (eg, ammonia, clotting factors) or clinical evidence of liver dysfunction	5	2.2
Severe	Rise (>50 times the normal value) in serum transaminases or biochemical or clinical evidence of liver failure	2	0.9%
Total		232	100.0

MAXPSS, Maximum Poisoning Severity Score; NPIS, National Poisons Information Service.

Paracetamol in overdose can lead to hepatotoxicity and death. IV paracetamol has the potential for more severe poisoning compared with overdose by ingestion as there is no enteral absorptive buffering the drug is immediately in the patient's circulation; it is often administered in patients with possible glutathione depletion; and may be administered to children with other risk factors including comorbidities. Neonates and nutritionally malnourished children may be at higher risk of hepatotoxicity.[5 6] The maximum licensed dose of IV paracetamol in the UK is 30 mg/kg/day for neonates and children weighing up to 10 kg, 60 mg/kg/day for children between 10 and 50 kg and 4 g/day for children over 50 kg in weight. The NPIS advises that a dose above 60 mg/kg of IV paracetamol over 24 hours requires action with acetylcysteine. There are few data regarding IV paracetamol poisoning in the paediatric population, except for several case reports.[5–8] No national UK data exist focusing on IV paracetamol poisoning in children.

AIM

We aimed to explore the epidemiological characteristics, severity and types of medication errors in IV paracetamol overdose in under 18 year olds in the UK reported to the NPIS over a 14-year period.

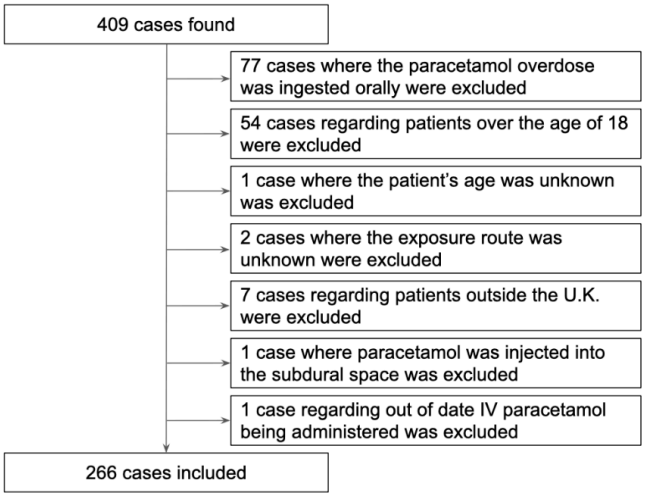

Figure 1 Flow diagram of cases from initial search.

METHODS

All telephone enquiries to the NPIS between 1 January 2008 and 31 December 2021, regarding children under 18 years of age subject to an overdose of IV paracetamol in the UK, were included. Specialists in poisons information deal with telephone enquiries with on-call NPIS consultants available to discuss complex cases. All calls are recorded and logged using the UK Poisons Information Database (UKPID).[9] Enquiries were extracted from the UKPID by searching for the following coding parameters: 'age' between 0 and 17 years; 'product ingredient' was 'paracetamol'; and 'exposure route' recorded as any of 'injection', 'intravenous', 'intramuscular' or 'subcutaneous' for further analysis. These cases were then individually reviewed to ensure coding accurately reflected the clinical case. Multiple enquiries regarding the same patient were condensed into a single case. Enquiries regarding patients from outside the UK and with only orally ingested overdoses of paracetamol were excluded. Cases where the age of the child was unknown and the exposure type was unknown were excluded.

The following variables were recorded: number of calls per year; number of calls per calendar month; age and sex of the child; overdose exposure type (acute, sub-acute, chronic, acute on therapeutic and staggered); Poison Severity Score (PSS); Maximum Poisoning Severity Score (MAXPSS); NPIS advice to administer acetylcysteine; whether the patient received more than 60 mg/kg of paracetamol in the 24-hour period; and what the error pattern was. NPIS define acute as 'a single exposure to a drug or chemical, irrespective of route'; sub-acute as 'either continuous exposure to a drug or chemical, or repeated (multiple) acute exposures to a drug or chemical, by any route, for more than 24 hours and less than 1 month'; chronic as 'either continuous exposure to a drug or chemical, or repeated (multiple) acute exposures to a drug or chemical, by any route, for more than 1 month'; acute on therapeutic as 'an acute dose taken by a patient on therapy with this medication' and staggered as 'several doses of the same drug taken over a period of more than 2 hours and less than 24 hours'. The PSS was recorded throughout the period. PSS is a validated grading system recording the severity of features around the time of the enquiry.[10] The MAXPSS reflecting the most severe features the patient had at the time of enquiry was first included as part of the enquiry logging process in 2010. Descriptive examples of the MAXPSS are shown in table 1 with a range from none to severe. Data were analysed using descriptive statistics.

The access frequencies regarding IV paracetamol to the NPIS-led toxicology information portal TOXBASE and its mobile app were analysed during the study period. Data for access frequencies to the website were available from 24 April 2010 onwards. Data for access frequencies to the app were available from 1 October 2015 onwards. TOXBASE users from NPIS centres; users within the 'educational' and 'government office' categories and users from outside the UK were excluded from the analysis. The frequencies may include accesses from the same session or individual and do not differentiate between adults and paediatric IV paracetamol TOXBASE access.

Ethical approval was not required in line with Health Research Authority guidance (http://www.hra-decisiontools.org.U.K./ethics/) as this study only used information collected routinely as part of usual clinical care and was passed to the researchers in a fully anonymised format.

Table 2 Number of accesses to TOXBASE online website and app per year

Year	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Online access frequency (n)	158	211	262	392	370	311	313	470	699	669	969	826
App access frequency (n)	N/A	N/A	N/A	N/A	N/A	6	13	36	78	158	203	276

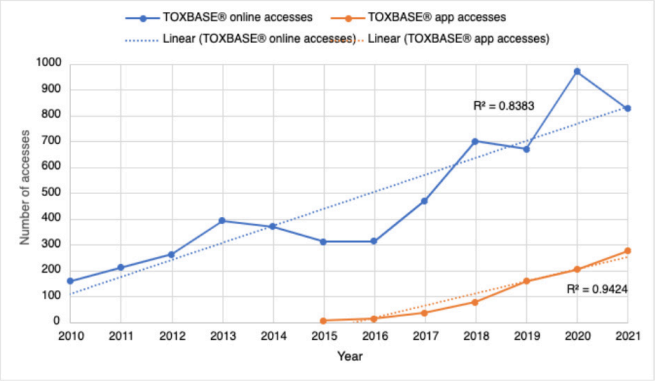

Figure 2 Number of accesses to the TOXBASE online website and app regarding IV paracetamol between 2010 and 2021

RESULTS

From the initial search output of 409 cases, 143 were excluded for the following reasons: oral paracetamol was ingested (n=77), the patient was over 18 years old (n=54), age was unknown (n=1), exposure route was unknown (n=2), patients were outside the UK (n=7); subdural administration (n=1); enquiry regarding out of date IV paracetamol being administered (n=1) (figure 1). Of the remaining 266 cases included in this study, there was a slight male preponderance (145 males; 114 females and 7 unknown). The numbers of enquiries regarding IV paracetamol overdose varied between 13 and 26 cases per year. Over half (n=145; 54.5%) involved children less than 1 year of age, with the incidence decreasing with age: 48 aged 1–4 years (18.0%), 49 aged 5–11 years (18.4%), 24 being 12–17 years of age (9.0%).

An acute overdose was the most common mode of exposure (n=125, 46.7%), with staggered overdose the second most common mechanism (n=99, 37.2%). There were 29 acute on therapeutic cases (10.9%) and 13 cases (4.9%) were classified as sub-acute overdoses.

From 2010 onwards, the MAXPSS was recorded and was available in 227 of the 232 cases after 2010 (5 unknown). The MAXPSS score ranges from 1 (asymptomatic) to 4 (severe symptoms). In 202 cases, the patient remained asymptomatic with a score of 0 (87.1%). The PSS was available for all cases (n=34) prior to 2010. In all 34 cases, the PSS was 0. Table 1 shows the MAXPSS.

The antidote acetylcysteine was recommended by NPIS in 113 cases (42.5%) and not in 121 (45.5%). It had already been given to 12 patients (4.5%) and in 20 cases (7.5%) its use was not known. In 105 cases (39.5%), the excess paracetamol dose given over a 24-hour period exceeded 60 mg/kg, which is the dose requiring action. In 110 cases (41.4%), the child received 60 mg/kg or less. The dose was not clear in 51 cases (19.2%).

The intended dose versus the administered dose was examined for any trends or common overdose patterns. There were 45 cases (16.9%) where a 10-fold overdose occurred. In 64 cases (24.1%), the caller was concerned about repeated as well as concomitant oral and IV dosing (ie, doses being given less than 4 hours apart, frequently due to a dose being given in theatre and subsequently given on the ward or vice versa). There were 4 cases (1.5%) where the weight of the child was incorrect and they inadvertently received an overdose. Other errors where the overdose pattern was not clear amounted to 153 cases (57.5%). NPIS does not routinely collect data on outcome, thus we were unable to report this.

The number of searches on the TOXBASE online website and app regarding IV paracetamol increased fivefold between 2010 and 2021 as seen in table 2 and figure 2. This demonstrated a positive linear trend on regression for both online accesses (R^2=0.84, p<0.001) and for app accesses (R^2=0.94, p<0.001).

DISCUSSION

Children under 1 year of age are most likely to have received IV paracetamol in excess resulting in a request for NPIS advice. These data suggest a range of systematic failures that resulted in inadvertent IV paracetamol overdose. Prescribing and administration errors are easy to make and have the potential for serious harm. Multiple overdosing errors due to errors in prescribing or administration are common in these patients with common error patterns including 10-fold overdoses as reported in other countries.[11 12] Similarly, inadvertent dual dosing by both oral and IV paracetamol occurred.

This is in keeping with the few published case reports which concerned neonates and infants.[7 8] Our study suggests that NPIS enquiry statistics can show useful patterns of medication errors. However, telephone enquiries probably under-represent the scale of the problem as healthcare professionals in the UK may manage these errors using advice from TOXBASE instead. The number of TOXBASE accesses to the IV paracetamol entry has increased significantly on both the website and the app version. This indicates an increasing need for information regarding toxicity of IV paracetamol.

NPIS does not routinely collect long-term follow-up data, however, it does follow-up some individual cases for particular clinical reasons. To address this limitation in our current study, we intend to propose a British Paediatric Surveillance Unit (BPSU) study to look at the outcomes of these children in terms of their morbidity, mortality and extended hospital stay.

By understanding more about the cause of medication errors, future errors might be reduced by introducing whole scale systematic changes. These advances could include the development or implementation of physician/nursing electronic prescribing support systems, and better recording and communication regarding doses of paracetamol and their administration. The use of a single drug chart/system to prevent intraoperative IV paracetamol doses being repeated on the post-operative ward seems advisable. The active consideration of other routes where a 10-fold overdose may be more obvious to the administrator compared with IV administration should be considered. Alternative routes if available should be used as they are safer due to buffering, less costly and produce less environmental waste. Finally, should the child warrant IV over enteral paracetamol administration, the supply of smaller vials (100 mg in 10 mL) for infants may mitigate against 10-fold errors.[13] Whole system changes in prescribing may lead to improvement and less IV paracetamol errors.

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