



Health Services Safety
Investigations Body

Investigation report

Unintentional paracetamol overdose in adult inpatients with low bodyweight

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Theme:

Medication

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Considerations in light of coronavirus (COVID-19)

A number of national investigations were in progress when the COVID-19 pandemic significantly affected the UK in 2020. Much of the work associated with developing the investigation reports necessarily ceased as HSIB's response was redirected.

For this national report, while the learning described has not changed due to COVID-19, the processes HSIB used to engage with staff had to be adapted. This included fewer face-to-face interviews and interactions and an increased use of virtual interviewing. Owing to the nature of this investigation there was no need to visit clinical areas to observe work in practice.

A note of acknowledgement

We would like to thank the Patient whose experience is documented in this report, and her family. We would also like to thank the healthcare staff who engaged with the investigation for their openness and willingness to support improvements in this area of care.

About this report

This report is intended for healthcare organisations, policymakers and the public to help improve patient safety in relation to prescribing oral paracetamol to adults with a low bodyweight (less than 50kg) who have been admitted to hospital. For readers less familiar with this area of healthcare, terminology and systems are explained in the 'Background and context' section.

Our investigations

Our investigators and analysts have diverse experience of healthcare and other safety-critical industries and are trained in human factors and safety science. We consult widely in England and internationally to ensure that our work is informed by appropriate clinical and other relevant expertise.

We undertake patient safety investigations through two programmes:

National investigations

Concerns about patient safety in any area of NHS-funded healthcare in England can be referred to us by any person, group or organisation. We review these concerns against our investigation criteria to decide whether to conduct a national investigation. National investigation reports are published on our website and include safety recommendations for specific organisations. These organisations are requested to respond to our safety recommendations within 90 days, and we publish their responses on our **website**.

Maternity investigations

We investigate incidents in NHS maternity services that meet criteria set out within one of the following national maternity healthcare programmes:

- Royal College of Obstetricians and Gynaecologists' 'Each Baby Counts' report
- MBRRACE-UK 'Saving Lives, Improving Mothers' Care' report.

Incidents are referred to us by the NHS trust where the incident took place, and, where an incident meets the criteria, our investigation replaces the trust's own local investigation. Our investigation report is shared with the family and trust, and the trust is responsible for carrying out any safety recommendations made in the report.

In addition, we identify and examine recurring themes that arise from trust-level investigations in order to make safety recommendations to local and national organisations for system-level improvements in maternity services.

For full information on our national and maternity investigations please **visit our website**.

Executive Summary

Background

This investigation explores the prescription of oral paracetamol in adult inpatients who, on admission to hospital, have low bodyweight (less than 50kg). It specifically focuses on the dose of oral paracetamol prescribed and given to this group of patients while in hospital, and the processes for ensuring weight is accurately recorded.

As an example, which is referred to as 'the reference event', the investigation considered the experience of Dora, an 83-year-old woman who weighed less than 50kg on admission and lost further weight in hospital. While in hospital, Dora was prescribed oral paracetamol 1g four times a day. Towards the end of her admission, Dora developed multiorgan failure due to sepsis and was diagnosed with paracetamol-induced liver toxicity.

The investigation's findings and safety observations aim to increase awareness of the potential for paracetamol toxicity in adults with low bodyweight. Some of the findings and conclusions may also be applicable to other medications that have the potential to cause harm in patients with low bodyweight.

The reference event

Dora was admitted to hospital following a fall at home. She had a longstanding lung condition that made her susceptible to infection. At hospital, Dora was found to have no injuries requiring treatment from her fall, but an X-ray showed infection in her lungs and she was admitted to a ward for antibiotic treatment. Dora's knee was sore following her fall, so a doctor prescribed 1g paracetamol, four times a day, to help with the pain.

Dora was weighed on day 12 of her admission and was 40.5kg; on day 20 she was 39.7kg; and on day 25 she was 37.0kg. Dora's prescription for paracetamol was not reduced until she was found to have liver toxicity on day 29.

During Dora's stay in hospital she did not always require the maximum dose of 4g oral paracetamol per day. Her last daily dose of 4g was on day 20, and after that she received between 1g and 3g every 24 hours. Dora underwent liver function tests while she was in hospital, which did not indicate liver damage until day 29. Paracetamol was stopped at this point. By this time, Dora was unwell with sepsis as a result of her lung infection.

Dora's paracetamol level was found to be significantly raised and treatment was started to correct this. Sadly, Dora died the day after the start of treatment. An inquest concluded that paracetamol-induced liver toxicity was a causal factor in her death.

The national investigation

The risk of oral paracetamol causing liver toxicity in adults with low bodyweight is recognised in the literature and in patient safety incident reports. HSIB contacted the hospital where the reference event occurred. The Trust welcomed HSIB's involvement and collaborated with information gathering.

Following initial information gathering and evaluation against the HSIB patient safety risk criteria (see section 3.2), the Chief Investigator authorised a national safety investigation.

Findings

Oral paracetamol is a widely used medication that has few side effects for most people.

- There is limited data on how oral paracetamol affects adults with low bodyweight.
- Although liver toxicity is a recognised risk with oral paracetamol, evidence regarding the relationship between low bodyweight and the risk of liver toxicity is unclear.
- Two independent bodies are contracted to provide oral paracetamol prescribing guidance for clinicians. The information provided is not consistent.
- There is potential for electronic prescribing and medication administration systems to prompt healthcare providers to record a patient's weight and consider liver toxicity in those who weigh less than 50kg.
- Environmental and other factors create challenges to the timely weighing of patients on a ward.

HSIB makes the following safety observations

Safety observation O/2022/151:

It may be beneficial for electronic prescribing and medication administration systems to include an alert for oral paracetamol that prompts documentation of a patient's weight and consideration of the risk of liver toxicity when their weight is less than 50kg.

Safety observation O/2022/152:

It may be beneficial for the evidence on oral paracetamol and low bodyweight to be reviewed by the relevant national bodies to reach a consensus and agree standardised prescribing guidance.

Safety observation O/2022/153:

It may be beneficial for available technological solutions, such as beds with built-in scales, to be used to weigh patients. However, the cost of such equipment makes its widespread adoption within the NHS challenging.

1 Background and context

1.1 Paracetamol

1.1.1 Paracetamol is one of the most widely used pain relievers in the world, both within and outside of hospital (Prescott, 2000). In the UK, individuals can buy paracetamol over the counter in pharmacies, supermarkets and other outlets.

1.1.2 Paracetamol is available in different preparations:

- Oral – administered as tablets, capsules, a liquid or effervescent tablets (dissolve in water).
- Rectal – administered as a suppository.
- Intravenous (IV) – administered through a cannula directly into the patient's bloodstream. IV paracetamol can only be administered by a qualified healthcare professional, usually in hospital.

1.1.3 Paracetamol has few side effects for most people, and is often the first-line treatment for mild to moderate pain for patients in hospital. It is available as a single-ingredient medicine or in combination with other ingredients. For example, co-codamol combines codeine and paracetamol. When taken at the recommended dose, paracetamol has a low risk of toxicity (harmful effect).

1.1.4 The British National Formulary (BNF) is an electronic and print reference that provides succinct information, for use at the point of care, on selecting, prescribing, dispensing and administering drugs. It includes information on indications for, and doses of, paracetamol (Joint Formulary Committee, 2020). In this report, low body weight is defined as under 50kg. There is a separate BNF for Children (BNFc) that provides dose information for children aged up to and including 17 years.

1.1.5 Paracetamol in excess is toxic to the liver, known as 'hepatotoxicity' or liver toxicity. It has a narrow therapeutic index, meaning that even small overdoses can potentially lead to harm (Dear et al, 2015). Therefore the British Liver Trust states that: 'The maximum dose [of paracetamol] within a 24-hour period must never be exceeded.' (British Liver Trust 2017).

Overdoses do occur, and can be intentional with suicidal intent or unintentional, such as taking or being prescribed an incorrect dose. The National Poisons Information Service (n.d.) provides information on managing overdoses.

1.2 Risk factors for liver toxicity from paracetamol

1.2.1 This HSIB report concerns the prescribing and administration of paracetamol to adult patients in hospital who are of low bodyweight. In this report, low bodyweight is defined as less than 50kg.

1.2.2 Paracetamol is broken down in the liver. One of its breakdown products is potentially toxic to the liver. Factors that increase the risk of liver toxicity from paracetamol include the presence of conditions that impair liver function. The BNF states:

‘Before administering, check when paracetamol [was] last administered and cumulative paracetamol dose over previous 24 hours; body-weight under 50 kg; chronic alcohol consumption; chronic dehydration; chronic malnutrition; long-term use (especially in those who are malnourished).’

(Joint Formulary Committee, 2020)

1.2.3 In a section titled ‘Cautions, further information’, the BNF also states:

‘Some patients may be at increased risk of experiencing toxicity at therapeutic doses, particularly those with a body-weight under 50 kg [...] Clinical judgement should be used to adjust the dose of oral and intravenous paracetamol in these patients.’

(Joint Formulary Committee, 2020)

1.2.4 Factors that increase the risk of liver toxicity from paracetamol are also discussed in the academic literature. A 2018 review explored factors that might increase risk, such as genetic differences, metabolic conditions, ethnicity, age, nutritional state, bodyweight, alcohol, medication interactions and chronic liver disease (Caparrotta et al, 2018). The authors concluded that there was a lack of good-quality evidence to determine the contribution of bodyweight to liver toxicity and ‘whether certain individuals have a greater propensity to develop liver injury [from paracetamol] than others’ (Caparrotta et al, 2018).

1.2.5 Despite the BNF cautioning that ‘some patients may be at increased risk of experiencing toxicity at therapeutic doses, particularly those with a body-weight under 50 kg’ (Joint Formulary Committee, 2020), the role of low bodyweight in adults is debated.

1.2.6 The academic literature describes case studies in which adults weighing less than 50kg have been harmed after taking recommended doses of paracetamol (Claridge et al, 2010). In 2016, NHS Improvement received reports of two deaths where the dose of IV paracetamol had not been reduced in patients with low bodyweight (NHS Improvement, 2017). The adult dose of IV paracetamol in the BNF is longstanding (from at least 2005) and reflects the Summary of Product Characteristics (SmPC) for paracetamol solution for infusion (Electronic medicines compendium, 2021). The SmPC recommends weight-based dosing for patients with bodyweight of less than 50kg. The 'Cautions' section of the paracetamol monograph in the BNF was updated in 2016; the further information statement (see section 1.2.3) was added, and additional cautions regarding bodyweight less than 50kg, chronic alcohol consumption and long-term use (especially in patients who are malnourished) were included.

1.2.7 While there is recognition that low bodyweight in combination with other factors increases the risk of liver toxicity with paracetamol (Abdulla et al, 2013), there is debate as to whether low bodyweight alone is a risk factor. In various case reports of harm from paracetamol, the patients were of low bodyweight and had other risk factors for liver toxicity, including hepatitis (that is, inflammation of the liver) and alcoholism (Claridge et al, 2010) and muscular dystrophy and malnutrition (Pearce and Grant, 2008). Clarity Informatics, which is involved in writing clinical guidance for primary care (see section 5.1.4) has liaised with the Medicines and Healthcare products Regulatory Agency (MHRA) regarding the risk of liver toxicity with paracetamol. Clarity Informatics summarised the conclusions of the MHRA as follows:

'A person's weight being less than 50 kg is not in itself an indication to reduce the dose of oral paracetamol, consideration should be given to lowering the dose in people with other conditions likely to pre-dispose them to liver damage from paracetamol.'

(Clarity Informatics commissioned by the National Institute for Health and Care Excellence, 2020)

1.2.8 The ongoing debate into the risk of low bodyweight with respect to paracetamol toxicity means there is limited guidance on whether paracetamol doses should be adjusted in such individuals; it has, therefore, been left to clinical judgement. The BNF provides dose adjustment for IV (injectable) paracetamol for adults weighing less than 50kg, but not for oral or rectal paracetamol (Joint Formulary Committee, 2020). Caparrotta et al (2018) concluded that:

'Although there is no good-quality evidence to suggest that the dose of oral paracetamol should be reduced for individuals weighing less than 50 kg, it seems illogical that the oral

recommendations differ from those for intravenous administration [...]' (Caparrotta et al, 2018)

As a result, some organisations have developed their own guidance for oral dose adjustment in people weighing less than 50kg.

1.2.9 In August 2020, Clarity Informatics commissioned by the National Institute for Health and Care Excellence (2020) updated its information for primary care practitioners on analgesia for mild to moderate pain. This update acknowledged the MHRA's conclusion that weight less than 50kg is not in itself an indication to reduce the dose of oral paracetamol. However – and in contrast to the MHRA – it recommended considering a dose reduction for oral paracetamol in patients with a bodyweight of less than 50kg and proposed doses that should be considered (Clarity Informatics commissioned by the National Institute for Health and Care Excellence, 2020).

1.2.10 Following HSIB's investigation, and prior to publication of this report, Clarity Informatics commissioned by the National Institute Health and Care Excellence further updated the information for primary care practitioners on analgesia for mild to moderate pain. The update removed the proposed doses to be considered in patient's with a bodyweight of less than 50kg bringing the guidance more in line with the information provided by the MHRA.

2 The reference event

This investigation used the following patient safety incident, referred to as 'the reference event', as an example of unintentional paracetamol overdose in adults with low bodyweight.

2.1 Details of the event

2.1.1 Dora was an 83-year-old woman who lived at home with her husband. Dora had a longstanding prescription from her GP for co-codamol 30/500mg (that is, codeine 30mg and paracetamol 500mg), one or two tablets to be taken four times day, to a maximum of eight tablets daily, for pain relief. This prescription had spanned several years.

2.1.2 Dora fell at home on 6 January 2020 and was referred to hospital on 8 January by her GP after a conversation with her Son. Dora had a number of long-term medical conditions, including bronchiectasis (which can make the lungs more vulnerable to infection).

2.1.3 In the emergency department Dora was prescribed paracetamol 1g, to be administered intravenously (through a vein), for knee pain following her fall. The investigation found no evidence that this was given to Dora it is not known why.

2.1.4 A chest X-ray requested in the emergency department showed that Dora had an infection in her lungs, for which she was admitted to a medical ward for antibiotic treatment. Her medication chart, completed by a junior doctor on the ward, included a prescription for paracetamol 1g four times a day to be given either orally or intravenously. The first dose was administered orally on the morning of 9 January 2020.

2.1.5 Dora's medication chart was reviewed by a pharmacy technician on 9 January, and no errors or omissions were identified.

2.1.6 Dora's general condition deteriorated over the next few days. On 14 January, blood results showed her kidneys were not functioning normally (acute kidney injury).

2.1.7 On 17 January 2020, Dora's antibiotics for her chest infection were changed as she was thought to have developed sepsis (an overreaction to infection causing damage to the body's own tissues and organs). The nursing records state that Dora was eating and drinking very little at this time, that she was finding it difficult to mobilise and that she was feeling generally unwell.

2.1.8 On 20 January 2020, the dietetic assistant reviewed Dora and requested her weight and food intake be monitored. Dora was weighed that day.

2.1.9 On 21 January, the medical records state that Dora was improving. She continued to have difficulty mobilising, for which she was receiving physiotherapy. Paracetamol and codeine were prescribed and administered regularly for her knee pain (see table 1).

2.1.10 On 22 January 2020, Dora was seen by a dietitian who documented her weight from 20 January on the electronic patient record as 40.5kg. The dietitian prescribed dietary supplements to help meet her nutritional needs.

2.1.11 Documentation in the medical records from 13 January onwards, shows that Dora felt nauseous and on occasions vomited blood. On 25 January blood tests were requested, one of which was to assess Dora's liver function.

2.1.12 Results from the blood sample taken on 25 January 2020 were available on 27 January. These showed that Dora's liver function was abnormal. Dora's alanine transaminase (ALT) was raised to 46U/L (expected range 10–35U/L) and alkaline phosphatase (ALP) was increased to 228U/L (expected range 30–130U/L). ALT is an enzyme that is released from liver cells if they are damaged. ALP is an enzyme in the liver that can be raised with some liver problems. Following these results, the doctor requested further investigations to assess Dora's liver function.

2.1.13 On 28 January, Dora was weighed again. Her weight, which was 39.7kg, was written on her medication chart. The investigation was unable to identify who weighed Dora; there was no documentation regarding this.

2.1.14 A member of the pharmacy team reviewed Dora's medication chart on 31 January 2020. They noted Dora's low bodyweight and asked for her dose of low-molecular-weight heparin (a medication to reduce the risk of blood clots forming) to be reduced. No change to the paracetamol dose was requested.

2.1.15 On 1 February 2020, Dora's medical records show that her kidney function had returned to normal, but that she still felt unwell and nauseated. Blood tests showed raised inflammatory markers; inflammatory markers can be raised for many reasons, including infection. That night, a nurse documented that Dora was "slightly muddled". This continued the following day, and was described as "confusion" by nursing staff in the medical records for that day. The confusion, along with the blood test results indicated that Dora's suspected sepsis was not resolving with treatment.

2.1.16 On 3 February 2020, Dora was reviewed by a gastroenterology consultant. The consultant documented that Dora had been confused all weekend and queried whether she may have developed a further infection. Dora continued to report feeling unwell and had no appetite. She was moved to a respiratory ward that evening.

2.1.17 On 6 February 2020, Dora remained unwell. At 17:05 hours the medical records state that her ALT level had significantly increased from her previous bloods taken on 4 February 2020 (from 28U/L to 567U/L on 6 February), indicating liver damage. Dora remained confused, and the junior doctor who was advised of these results talked to their senior colleague about possible causes of the liver damage. The junior doctor was advised to stop Dora's paracetamol, repeat her blood tests in the morning and organise further investigations to assess her liver function. A nurse documented that Dora was in liver failure, with an international normalised ratio (INR) of 2.9. The INR is a calculation that gives an indication of clotting in the blood based on prothrombin, which is produced by the liver. The expected value for the INR is 1; anything above that can be a marker of liver failure or damage.

2.1.18 The following day, 7 February, Dora was documented to be in pain, confused and jaundiced (that is, she had a yellow skin colour, which is common with liver failure). In addition, her stomach was described in the medical records as firm and painful when touched.

2.1.19 A blood test showed that Dora's paracetamol level on 7 February was 42mg per litre, which – given the timing of her last paracetamol dose – indicated a significant paracetamol overdose. At 11:10 hours the medical team prescribed N-acetyl cysteine (NAC) which is a treatment for paracetamol overdose. Dora was seen by a consultant at 12:40 hours. The consultant documented 'suspect likely paracetamol-induced hepatitis' and to 'continue IV NAC'.

According to prescription chart, NAC had not been started at this point. NAC was administered as an IV infusion at 21:00 hours, almost 10 hours after the requirement was identified (see section 4.4).

2.1.20 Dora continued to deteriorate despite the administration of NAC, and sadly died on 8 February 2020.

2.1.21 Dora's death was referred to the coroner. An inquest was held on 4 March 2021, and the coroner concluded that Dora's "prescription of paracetamol was higher than it should have been and this played a part in her death".

2.1.22 The coroner listed the direct causes of Dora's death to be as follows:

- multiple organ failure with bronchopneumonia
- paracetamol-induced hepatotoxicity
- fall on 8 January 2020 with left knee pain, treated by paracetamol and codeine.

2.1.23 Dora's general frailty and bronchiectasis were listed as other significant conditions that played a role in her death.

Table 1 Details of the doses and dates on which paracetamol was administered to Dora

Date (all 2020)	Number of 1g paracetamol doses administered	Reason for missed doses	ALT (U/L)	Weight (kg)	Additional information
8 January	0	Not documented	14		
9 January	4				
10 January	4				
11 January	4				
12 January	4				
13 January	3	Patient refused			Patient felt very sick
14 January	3	Nil by mouth/ vomiting			Nausea, vomiting
15 January	4				
	3	Not documented			

Date (all 2020)	Number of 1g paracetamol doses administered	Reason for missed doses	ALT (U/L)	Weight (kg)	Additional information
16 January					
17 January	4				
18 January	4				
19 January	4				
20 January	4			40.5	
21 January	4				
22 January	3	Patient refused			
23 January	4		49		Vomiting blood, no abdominal pain
24 January	4				Medication chart rewritten
25 January	2	Patient refused	46		Nausea
26 January	3	Patient refused			Nausea
27 January	4		38		
28 January	4			39.7	
29 January	3	Patient refused			
30 January	2	Patient refused			
31 January	1	Patient refused	25		Pharmacy review – heparin dose reduced in view of bodyweight
	3				

Date (all 2020)	Number of 1g paracetamol doses administered	Reason for missed doses	ALT (U/L)	Weight (kg)	Additional information
1 February		Withheld; reason not documented			Patient became confused
2 February	2	Patient refused		37.0	
3 February	2	Patient refused			Transferred to respiratory ward
4 February	2	Withheld; reason not documented	28		
5 February	2	Withheld; reason not documented			
6 February	1	Remaining doses crossed through	567		
7 February	0	Not prescribed	626		
8 February	0	Not prescribed	450		Patient died

2.2 Impact

2.2.1 The HSIB investigation sought an independent clinical opinion from a subject matter advisor (SMA). Specifically, the SMA was asked about the impact on Dora of the oral paracetamol she was administered. The SMA's opinion was informed by information provided by the investigation, review of Dora's medical records, and their knowledge and expertise regarding acute liver failure. In the SMA's opinion, given Dora's multiorgan failure from sepsis, any dose of paracetamol was likely to be toxic to the liver as the liver was not functioning normally at this time.

2.2.2 The SMA noted that prior to her diagnosis with sepsis, Dora had been tolerating 1g paracetamol four times a day, as evidenced by blood tests taken throughout her admission. These blood tests did not demonstrate a negative effect of the paracetamol on Dora's liver. Thus, it appears that Dora's sepsis, rather than her low bodyweight, led to liver toxicity from paracetamol.

3 Involvement of the Healthcare Safety Investigation Branch

This section outlines how HSIB was alerted to the issue of unintentional overdose of paracetamol in adult inpatients with low bodyweight on admission to hospital. It also describes the criteria HSIB used to decide whether to proceed with the investigation, and the methods and evidence used in the investigation process.

3.1 Notification of the reference event and decision to investigate

3.1.1 HSIB received a referral from a hospital trust following the death of an adult patient of low bodyweight who had developed liver toxicity, likely due to paracetamol. Following a review of the case and relevant literature, HSIB launched a full investigation. As considerable time had passed since the death of the Patient in the referral case, the investigation identified a more recent, similar incident where staff were likely to have greater recall of events.

3.2 Decision to conduct a national investigation

3.2.1 HSIB conducted an initial scoping investigation, which determined that the patient safety concern met the criteria for a national investigation (see below). HSIB's Chief Investigator authorised a national investigation.

Outcome impact – what was, or is, the impact of the safety issue on people and services across the healthcare system?

3.2.2 Overdose of paracetamol causes liver toxicity, which can lead to death or significant harm, such as acute liver failure, jaundice, bleeding, and neurological and psychological issues (Rotundo and Prysopoulos, 2020). Even recommended doses of paracetamol in some seemingly fit people have shown evidence of effects on the liver (Weiler et al, 2015; Bataller, 2007; Watkins et al, 2006). Patients with low bodyweight may be at increased risk of liver toxicity from paracetamol (Clarity Informatics commissioned by the National Institute for Health and Care Excellence, 2020).

Systemic risk – how widespread and how common a safety issue is this across the healthcare system?

3.2.3 Unintentional paracetamol overdoses are regularly reported to the National Reporting and Learning System – the central database of patient safety incident reports in England and Wales. However, the issue is thought to be under-recognised (Ganger et al, 2018; Khandelwal et al, 2011). Unintentional overdoses in hospital might result from (Niedrig et al, 2016; Charpiat et al, 2012):

- prescription and/or administration of paracetamol without accounting for a person's individual risk factors, including low bodyweight
- prescription and/or administration of paracetamol when a person has recently received paracetamol or is already taking another paracetamol-containing medicine.

3.2.4 In one Swiss hospital study, 6% of people prescribed paracetamol were exposed to administration above the recommended dose in at least one 24-hour period (Niedrig et al, 2016).

Learning potential – what is the potential for an HSIB investigation to lead to positive changes and improvements to patient safety across the healthcare system?

3.2.5 There is limited literature on the wider system factors that hinder safe prescribing of paracetamol to adults with low bodyweight in a hospital setting. An HSIB investigation could help fill this knowledge gap and identify opportunities to mitigate the risk.

3.3 Evidence gathering

3.3.1 Evidence gathered in this investigation included the following:

- A review of the Patient's clinical records, and of the Trust's policies, procedures, audit results and practice regarding paracetamol prescribing.
- Telephone conversations with the Patient's Son.
- Interviews with 10 staff at the Trust where the reference event occurred.
- A review of the Trust's internal serious incident investigation report.
- A review of the literature relevant to the safety risk.
- Interviews, telephone calls and email correspondence with representatives from the British National Formulary, Clarity Informatics, Medicines and Healthcare products Regulatory Agency, National Institute for Health and Care Excellence, National Poisons Information Service, Care Quality Commission, NHS Supply Chain and British Association for Parenteral and Enteral Nutrition (BAPEN).

3.3.2 The investigation was conducted between November 2020 and October 2021. The COVID-19 pandemic, and the need for hospitals to focus efforts on responding to the third wave, resulted in a 3-month pause in the investigation.

3.4 Analysis of evidence

3.4.1 The investigation used a model called the Systems Engineering Initiative for Patient Safety (SEIPS) to analyse the gathered evidence (Holden et al, 2013; Carayon et al, 2006). SEIPS provides a human factors framework for understanding the work system (that is, the external environment, organisation, internal environment, tools and technology, tasks and persons), work processes (including physical, cognitive and social/behavioural aspects) and the relationship between these and the resulting outcomes in healthcare. Figure 1 shows the aspects of the work system that were explored as part of the investigation.

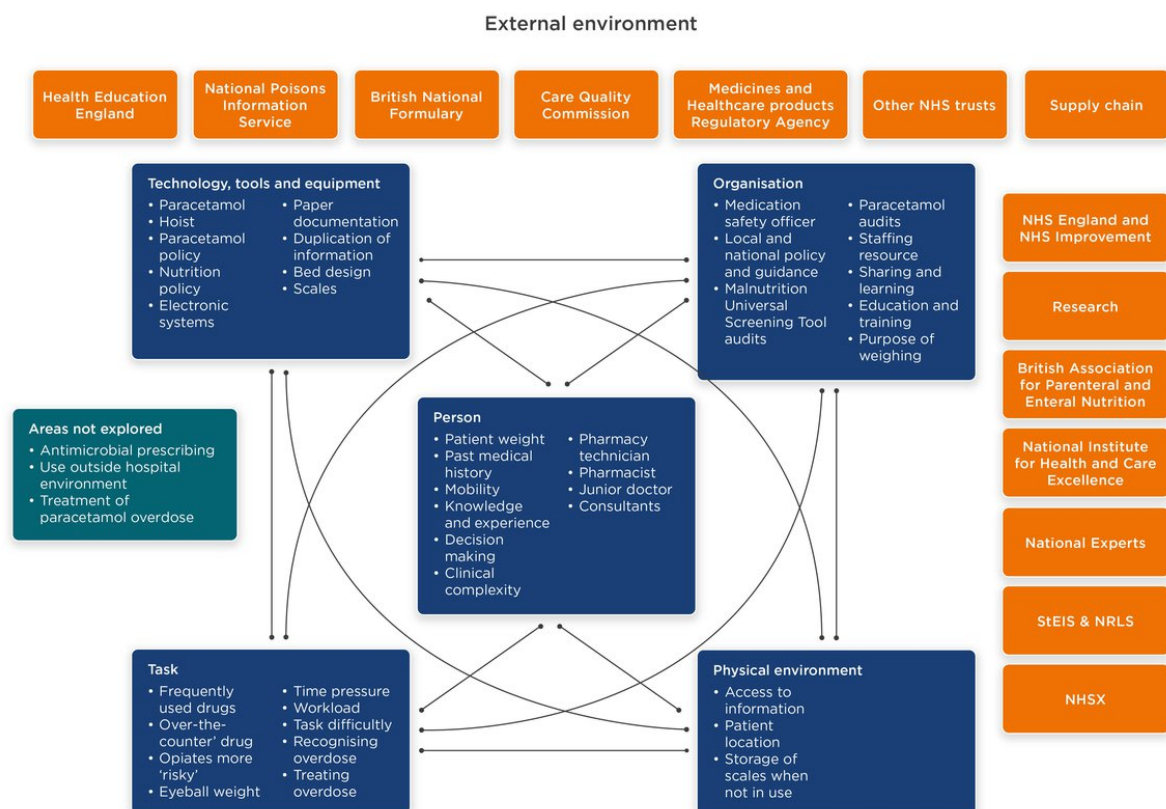


Figure 1 SEIPS model

3.4.2 After contributory factors had been identified, the investigation plotted them on an AcciMap (Rasmussen, 1997), which was used to visualise the work system. An AcciMap allows factors across the overall system of activity (including regulatory levels) to be taken into consideration, and factors can be linked both within and across different levels (see figure 2).

3.4.3 The findings were shared with the stakeholders identified by the investigation. This enabled checking for factual accuracy and overall sense-checking. The stakeholders contributed to developing the safety recommendations based on the evidence gathered.

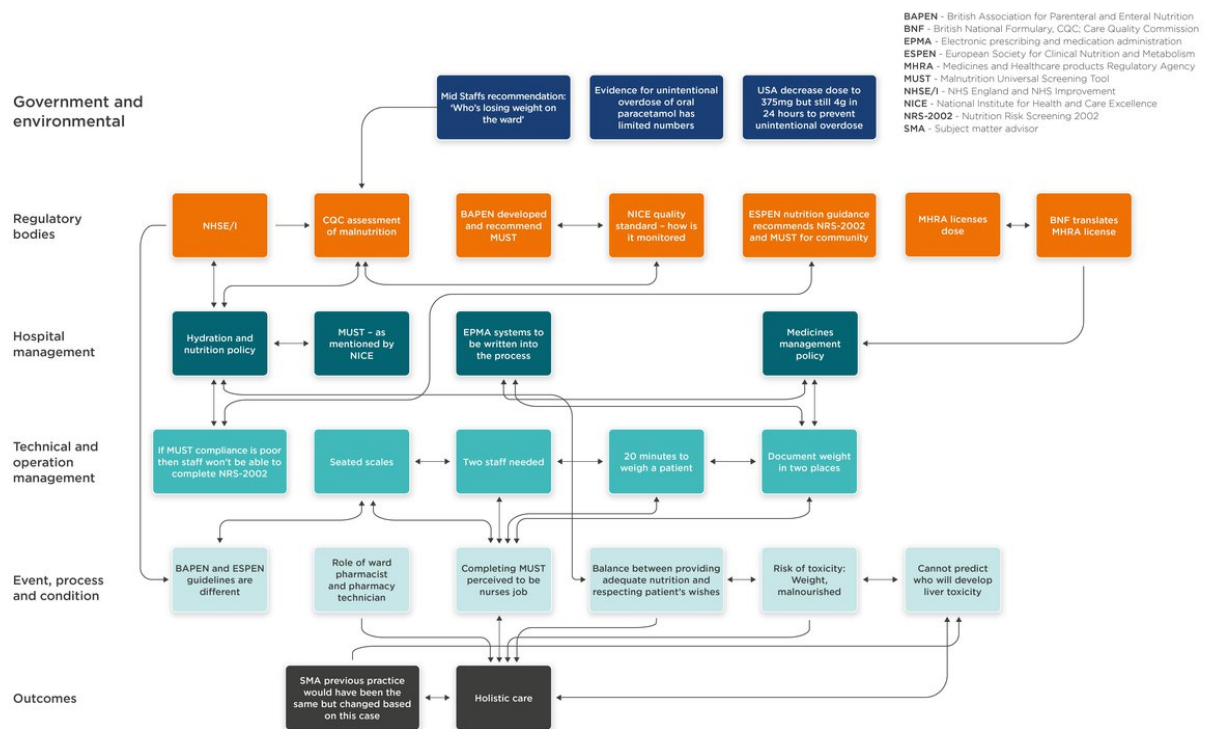


Figure 2 AcciMap

4 Analysis and findings – the reference event

This section describes the investigation's findings in relation to the reference event. It focuses on the systemic factors that contributed to Dora's unintentional overdose of paracetamol and that influenced staff decisions and actions.

The findings are presented under the following headings:

- perception of risk
- identification of an underweight patient
- role of the pharmacy team
- response to paracetamol overdose.

4.1 Perception of risk

4.1.2 The investigation found that the risks associated with prescribing paracetamol to adults with low bodyweight were not fully appreciated by the hospital and primary care staff interviewed.

4.1.3 Before Dora's admission to hospital, she had a repeat prescription for co-codamol from her GP for pain relief. Co-codamol combines paracetamol 500mg (the same dose as in a paracetamol tablet) and codeine 30mg in a single tablet. Dora was prescribed co-codamol at a dose of one or two tablets (0.5–1g) four times a day, with a maximum dose of eight tablets in 24 hours. The GP said that Dora's weight was recorded in 2017 and was documented to be 35kg. The prescription of co-codamol – and therefore paracetamol – was not adjusted for Dora's weight.

4.1.4 A supply of 100 co-codamol tablets was given on each prescription. If the maximum of eight tablets a day had been taken, the supply of 100 tablets would last 12.5 days. The investigation found that Dora was requesting a repeat prescription approximately every 4 months, indicating that she was taking less than one tablet a day. The GP was not aware of how often Dora was requiring co-codamol for pain relief. The last prescription was supplied on 26 June 2019, 6 months before Dora's admission to hospital. At a medication review following this last prescription, the GP said that the repeat prescription for co-codamol had been discontinued and it was documented that it was no longer required.

4.1.5 Reflecting on the co-codamol prescribing for Dora, the GP said that it highlighted the importance of considering a patient's weight. The GP said it was "just luck" that Dora had not taken the full dose prescribed and received an unintentional overdose of paracetamol.

4.1.6 Hospital staff had similarly not appreciated the risk of paracetamol overdose in underweight patients. Dora was in hospital for a month and, during this time, there does not appear to have been any consideration of reducing the paracetamol dose prescribed in light of her small stature before 6 February 2020, when her blood results showed liver damage.

4.1.7 The investigation identified contributory factors that contributed to staff's perception of paracetamol as a largely risk-free medication. Staff told the investigation that paracetamol is given frequently to many patients on a daily basis and is not a medication they perceive as high risk. It appeared that this was reinforced by the fact that, unlike most medications prescribed in hospital, paracetamol is available over the counter and can be bought in many types of shop, including supermarkets, petrol stations and off-licences.

4.1.8 When asked which medications pose the greatest safety risk to patients, most staff interviewed said opiates (medications containing morphine and similar substances). In contrast, comments about paracetamol prescribing were summed up by one staff member as “blasé”. Another said: “Culturally, you don’t think ‘What’s the patient’s bodyweight?’ It just gets prescribed as a blanket 1g [of paracetamol].”

4.1.9 Staff perceptions that paracetamol posed no risk for Dora may have been influenced by the fact that prior to her hospital admission, Dora had been prescribed 1g paracetamol four times a day by her GP. During interviews, hospital staff referred to this as a factor in their perception that Dora was not at risk.

4.1.10 In contrast to the majority of staff, one junior doctor told the investigation that they were very aware of the risks of paracetamol-induced liver toxicity and, before prescribing paracetamol, would always ask the following: Does the patient weigh over 50kg? Is their liver function normal? Are they in hospital because of paracetamol overdose? When asked how this habit had formed, they could not recall but said that information they had either read or been told about paracetamol toxicity had ‘somehow stuck in their head’. They stated this was their individual practice and one they thought was not widely shared by colleagues.

4.1.11 Nursing and pharmacy staff said that since the reference event, there had been Trust-wide communication about the risks of paracetamol toxicity in patients with low bodyweight. Nursing staff said that this communication, and learning from the experience of this Patient, had changed their perception of paracetamol and that they were now very aware of the need to adjust the dosage in patients with low bodyweight (less than 50kg).

4.1.12 The investigation was mindful that the staff interviewed had worked on the ward where the reference event occurred. Whether this increased awareness of risk was common across staff on other wards and other clinical areas is not known.

4.1.13 The investigation considered the perception of paracetamol as a low-risk medication to be a significant contributory factor in the reference event and a systemic safety issue. This is explored further in the wider investigation (see section 5)

4.1.14 The Trust had a ‘clinical guideline for the use of paracetamol in adults and children’. The Medication Safety Officer stated they had heard of an incident in another hospital in which an inpatient patient had unintentionally received an overdose of paracetamol, and felt they needed to reflect the learning within their own trust. This prompted the guideline above. However, when the investigation asked staff about medicines policies they find useful or reach for, this guideline was not mentioned. The guideline says to consider a reduced dose of 500mg in frail older adults and adults with a bodyweight of less than 50kg. The investigation was not able to ascertain from the evidence whether a reduced dose was considered as per the guideline.

4.1.15 For staff to access the above guideline, they would need to be aware of its existence and to know they needed support or additional information in relation to prescribing paracetamol. However, as described above, there was a low perception of risk when prescribing paracetamol, and the frequency of paracetamol prescribing is likely to mean staff rarely consider the need to look for a guideline to assist with its prescribing.

Summary

4.1.16 Paracetamol is frequently given to patients in hospital and is readily available to the general public. This wide accessibility has influenced the perception of paracetamol as a low-risk medication.

4.1.17 Dora had previously been prescribed paracetamol by her GP (1g paracetamol four times a day at home), so the in-hospital prescription was not a new one.

4.1.18 The reference event and subsequent communication regarding the risk of paracetamol appears to have altered the perception of risk among the staff interviewed.

4.2 Identification of an underweight patient

4.2.1 To safely prescribe paracetamol, three elements are important in relation to weight:

- Establishing a patient's weight.
- Recording the weight on the medication chart.
- Using the documented weight to inform paracetamol dosing.

4.2.2 Each of these elements is discussed below.

Establishing Dora's weight

4.2.3 The investigation found no evidence that Dora was weighed until 20 January 2020, 12 days after her admission.

4.2.4 Evidence from staff interviews suggested that weighing a patient was a low-priority task compared with other clinical measurements, such as measuring their heart rate and blood pressure.

4.2.5 Evidence from staff interviews identified systemic barriers to the timely weighing of patients. These included aspects to do with the task, equipment availability and workload.

- Task – if a patient is unable to mobilise independently then two staff are needed to help the patient to use the scales. Dora had reduced mobility, and the help of one or two nurses was required for her to be weighed. While the task of weighing a patient may seem easily

achievable, the investigation was told that it could often take 15–20 minutes. The Head of Dietetics said that the practicality of weighing a patient each week can be difficult for busy wards, who often pick a day of the week or a day per bay to weigh patients. Patient weighing can therefore be difficult to achieve among the many other tasks required for patient care.

- Equipment availability – although a hoist would generally be available on a ward, it may be in use with another patient at the time when two staff are available and thus the window of opportunity can be lost.
- Workload – many tasks need to be carried out as part of patient care, resulting in competing priorities. Tasks such as checking intravenous medications for administration and helping a patient to the toilet/bathroom require more immediate action than weighing a patient. This means that on a busy ward, less urgent tasks – such as weighing a patient – can be delayed.

4.2.6 Evidence gathered by the investigation did not identify the reason(s) for the delay in Dora being weighed. While staff mentioned the influencing factors detailed above, it seemed that staff had not recognised it was an outstanding task.

4.2.7 The investigation was told that the “vast majority” of patients in hospital weigh more than 50kg. Dora was, therefore, unusual in this regard. When asked about the significance of weighing patients, some staff said they could look at a patient at the bedside and accurately judge whether they weighed less than 50kg. Staff described Dora as being slight in build and frail, but the possibility of her having a particularly low bodyweight – and the significance of this in relation to her prescribed medications – did not seem apparent to them. This comment from one staff member was characteristic:

“She was a typical patient, if you like. She was elderly, frail. I wouldn’t say she was overly small, but she wasn’t of large build either.”

Recording Dora’s weight on the medication chart

4.2.8 Dora’s weight was not documented on the medication chart until 28 January 2020, 20 days after her admission, when she was weighed for a second time (the first weighing was recorded on the electronic patient record only).

4.2.9 At the time of the reference event, the Trust ‘medicines policy’ included a requirement to record a patient’s weight on their medication chart. This requirement was relatively new, having been added to the policy in March 2019. The medication chart included a dedicated weight box

for this purpose. However, the investigation was told by staff that a patient's weight was not consistently recorded as it was not seen as a priority piece of information, compared with, for example, recording allergy status.

4.2.10 As well as being a requirement of the Trust's medicines policy, recording a patient's weight was also required by the Trust's 'nutrition and hydration policy'. This policy aims to identify a patient's risk of malnutrition, which is expected to be assessed within 24 hours of admission and weekly thereafter. The policy asks for a patient's body mass index (BMI) to be calculated. In order to calculate this, the weight of the patient must be known. Thus, a patient's weight should be recorded on admission and every week, and this information should be entered into the Trust's electronic patient record.

4.2.11 The requirement for a patient's weight to be obtained to calculate their BMI has been Trust policy since 2010. The Head of Dietetics stated that compliance was

"not great when MUST [Malnutrition Universal Screening Tool] was implemented in 2010, but over the years there has been an improved picture overall".

The Trust's audit of compliance with the nutrition and hydration policy showed that a score for risk of malnutrition was given 70% of the time on most wards. Weight was often documented as reported by the patient/carer rather than being measured on the ward, meaning compliance with weighing patients was lower.

4.2.12 Evidence from staff interviews highlighted task and technology factors that served as barriers to the timely documentation of weight. These included:

- Duplication of effort – patients weighed to calculate their BMI as part of the nutrition and hydration policy have their weight recorded in the Trust's electronic patient record. Staff would need to access this and transcribe the weight onto the paper medication chart.
- Information layout – there are multiple bits of information required on the medication chart, and the requirement for weight is not visually commanding among the other bits of information required. Furthermore, as discussed above, weight appeared not to be perceived as a priority item, compared with, for example, allergy status.

4.2.13 Staff told the investigation that they believed the electronic prescribing and medication administration (EPMA) system that the Trust was about to implement would mitigate the risk of a patient's weight not being recorded, as weight could be set up as a mandatory field. With this in place, the system could both prompt recording of weight and flag risks associated with weight-dependent prescribing. Such interventions are system focused (see section 4.2.16) and likely to be more effective in mitigating risk than relying on the vigilance and diligence that are

necessary with paper-based systems. However, while EPMA systems have some flags inbuilt, they are unlikely to cover all potential risks and scenarios. For example, Dora's GP used an electronic system for storing healthcare information and prescribing, but it did not include an alert linking weight and paracetamol (or paracetamol-combination medications) prescribing. During their interview with the investigation, the GP simulated prescribing 1g paracetamol four times a day for a patient weighing 35kg, and the system did not alert this as a risk. Thus, EPMA or other electronic systems will not of themselves mitigate risk, and alerts need to be added to address identified risks.

4.2.14 Any alerts would need to be implemented using ergonomics principles and be appropriately evaluated to ensure their effectiveness and reduce the risk of alert fatigue. In addition, while a mandatory weight field might be helpful in ensuring weight is documented, the circumstance of emergency situations would need to be considered as such a requirement could be counterproductive on such occasions. To reduce duplication of effort, it might also be helpful to explore options to ensure there is an automated link between a system's electronic patient record and the EPMA.

HSIB makes the following safety observation

Safety observation O/2022/151:

It may be beneficial for electronic prescribing and medication administration systems to include an alert for oral paracetamol that prompts documentation of a patient's weight and consideration of the risk of liver toxicity when their weight is less than 50kg.

4.2.15 Following the reference event, the Medication Safety Officer revised the medicines policy to include the requirement to weigh patients within 24 hours of admission and weekly thereafter. However, the six frontline clinical staff interviewed said they mostly used online tools and national prescribing guidance to guide their practice, rather than referencing Trust's medicines policy. None could recall a situation in which they sought advice directly from Trust medicines policy. It is not known if these staff are reflective of the majority of clinical staff or unusual in that regard. However, their evidence raises concerns about the effectiveness of the Trust's safety action to mitigate the risk of a patient's weight not being documented on the medication chart.

4.2.16 The concept of a 'hierarchy of effectiveness' (see figure 3) can be used to describe the properties associated with interventions. Certain interventions are more effective than others. The hierarchy of effectiveness approach states that system-focused interventions are more

effective at managing risk than people-focused interventions. A change in policy (as described above) is a people-focused intervention, and is therefore likely to be less effective than a system-focused intervention.

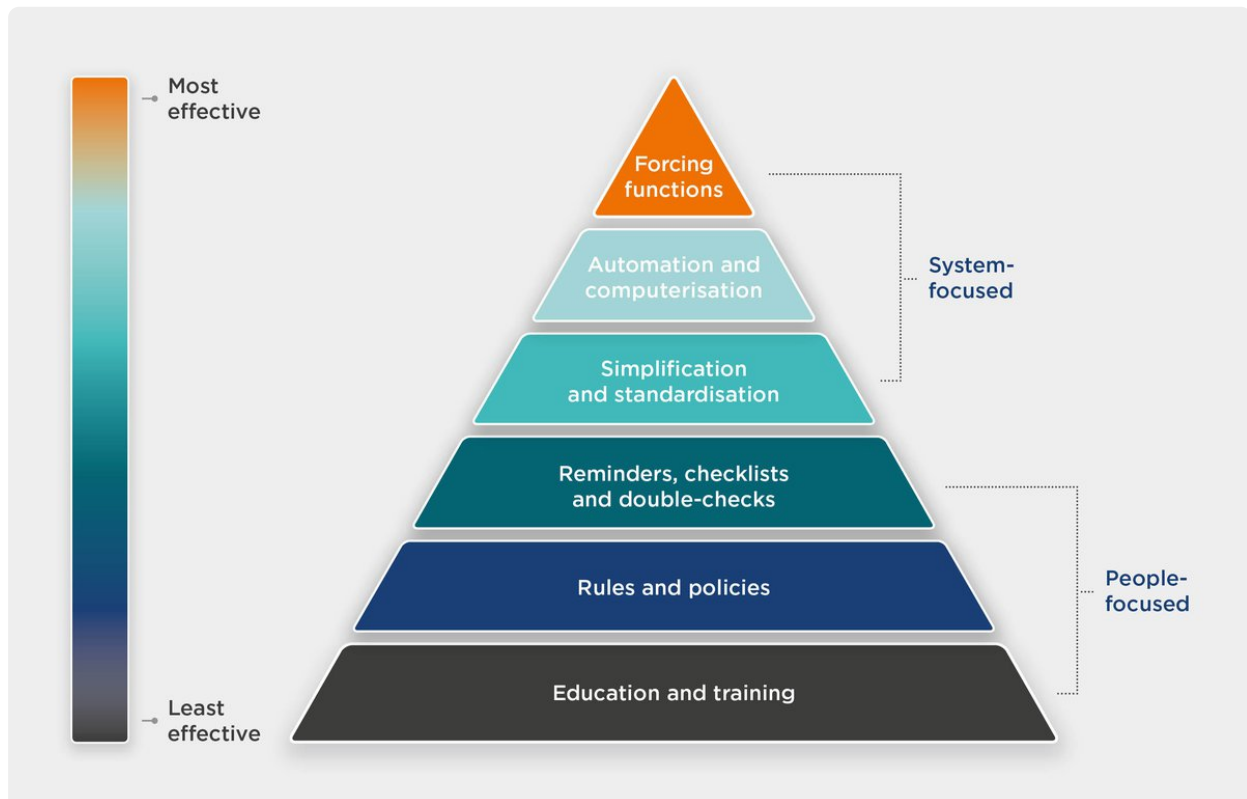


Figure 3 Hierarchy of effectiveness

Using the documented weight to inform paracetamol dosing

4.2.17 Dora's weight did not inform the dose of paracetamol she was prescribed. The dose was not altered until her blood results showed she had liver toxicity on 6 February 2020, 29 days after admission.

4.2.18 The investigation was told that even if weight is recorded on the medication chart in the designated section, staff may not notice or pay attention to it to inform paracetamol prescribing. One doctor said that allergy status is often not attended to, "let alone" the weight of a patient, highlighting the relative importance of allergy status compared with weight. Reflecting this doctor's comment, although Dora's weight was documented on the medication chart from 28 January 2020 onwards, this did not influence her paracetamol dose. Dora's weight would have been observable by the doctors, pharmacists and nurses involved with her care – the latter offering paracetamol four times a day during routine medication rounds. Thus, information being available does not guarantee it being used in decision making.

4.2.19 For information to guide decisions, the prescribing clinician would need to pay attention to the patient's weight and cognitively make the link between that and the need to adjust medication doses accordingly. In the reference event, a member of the pharmacy team made the link between Dora's low bodyweight and the need to reduce the dose of one of her prescribed medications (low-molecular-weight heparin), but did not make the link for paracetamol. In interview, they said they did not know why the need to reduce the paracetamol dose had not occurred to them. It is possible that the perception of heparin as a higher-risk medication than paracetamol accounted for the attention given to this medication.

4.2.20 The Trust undertook an audit of paracetamol prescribing practices 9 months after the reference event. The audit found 82% compliance with the British National Formulary (BNF) paracetamol dosing guidance for intravenous paracetamol. Oral doses of paracetamol were not reviewed, so compliance with BNF guidance for this route is not known. The investigation considered that including compliance with the dosing guidance for oral paracetamol would be beneficial for future audits.

4.2.21 The Trust told the investigation it had requested an inbuilt alert for the new EPMA system. The alert will flag to the prescriber if a patient's bodyweight is less than 50kg and they have been prescribed paracetamol more than 500mg four times a day. One staff member said they had used an EPMA system in a different trust and found alerts helpful when prescribing medications.

Summary

4.2.22 Dora was not weighed until 12 days after her admission and her weight was not recorded on the medication chart until 28 days after admission.

4.2.23 Once documented, Dora's weight did not inform the dose of paracetamol prescribed.

4.2.24 Barriers to weighing patients include task, workload and equipment factors.

4.2.25 Staff believed EPMA systems would be able to prompt the requirement for a patient's weight and alert the prescriber to the risk of paracetamol-related liver toxicity in a patient with low bodyweight.

4.3 Role of the pharmacy team

4.3.1 Pharmacy teams include pharmacists and pharmacy technicians. Pharmacy technicians are registered healthcare professionals who work under the supervision of a pharmacist. Pharmacists and pharmacy technicians have a number of safety roles to help ensure that patients on a ward receive the right medications at the right dose. The role of the ward

pharmacist has been previously investigated in HSIB's report into 'The role of clinical pharmacy services in helping to identify and reduce high-risk prescribing errors in hospital' (Healthcare Safety Investigation Branch, 2020).

4.3.2 One safety activity of the pharmacy team is to check medication charts to identify errors and omissions in prescribing. The investigation heard that the safety role of the pharmacy team provides reassurance to staff. The comments heard can be summed up in this remark from a junior doctor, who said they rely on the pharmacy check: "Once you see the [pharmacy] squiggle, you know it's ok." The 'pharmacy squiggle' refers to the pharmacist's signature, indicating that they have reviewed the medication chart and are content that it is correct for that patient.

4.3.3 The investigation found that this safety measure did not result in the paracetamol dose prescribed for Dora being highlighted for review. The dose was not outside that in the BNF, which advises caution rather than specific weight-related dose reductions (see section 5.1.6).

4.3.4 Dora's medication chart was reviewed by a member of the pharmacy team on 9, 22 and 31 January 2020. Dora's weight was not documented on her medication chart when the first two of these reviews took place. The first review, on 9 January 2020, was undertaken by a pharmacy technician. One purpose of this first review of a patient's medication chart is to identify any discrepancies between medications prescribed for a patient in hospital and those prescribed by a patient's GP, to take at home. This is known as 'medicines reconciliation'. Another purpose of this review is to identify if any medication required by the patient is not part of the ward medication supply and needs to be brought from main pharmacy to the ward. A further activity of the pharmacy technician during this review is to transcribe medication prescriptions from the handwritten medication chart into an electronic pharmacy system as part of stock management.

4.3.5 Both the medication chart review and transcribing into the electronic pharmacy system can be desk-based and do not necessarily involve interaction with the patient. On such occasions, unless the patient's weight is documented, there is no opportunity to identify whether the patient is under- or overweight – for example, by visually assessing the patient at their bedside. Although visually assessing a patient will not necessarily prompt concerns about weight, it does provide an opportunity for this.

4.3.6 When Dora's medication chart was reviewed by a pharmacist on 31 January 2020, they saw Dora's documented low bodyweight and recognised that her prescribed dose of low-molecular-weight heparin needed to be reduced as a result. The investigation was unable to identify why the staff member did not make the same connection regarding the prescribed dose of paracetamol.

4.3.7 In addition to medication chart checks by the pharmacy team, patients' medication charts may form part of the daily review by the multidisciplinary team. The Medication Safety Officer explained that pharmacy checks are also undertaken when there is a change made to a patient's medication. A review of Dora's medication chart showed new medications were prescribed on 9, 11, 14, 17, 21 and 30 January and 4 February 2020. The investigation found that there was no systemic process for flagging to the pharmacy team that a change had occurred and review was required. The onus was on the vigilance and diligence of the pharmacy team to review patient medication charts – ideally on a daily basis – to identify changes made.

4.3.8 While medication charts are regularly reviewed by the pharmacy team, it may not be the same person every time. The investigation was told that the team has a high workload, meaning that attention will be given to medication changes rather than re-review of all previously prescribed (and pharmacy-reviewed) medications. This means that errors in prescribing that are not picked up during the initial review are unlikely to be picked up in a later one.

Summary

4.3.9 Pharmacy teams play a key safety role in identifying errors and omissions in prescribing for patients. Evidence gathered by the investigation indicated that medical staff were reliant on pharmacy teams identifying errors.

4.3.10 Review of medication charts by the pharmacy team is often largely a desk-based activity. Therefore, the weight of the patient needs to be documented for it to inform appropriate dose adjustments.

4.3.11 Dora's weight, when documented, did not trigger a review of the paracetamol dose prescribed. However, the BNF advises caution rather than a weight-related dose reduction.

4.4 Response to paracetamol overdose

4.4.1 The investigation found there was a delay in responding to Dora's significantly raised paracetamol level once it had been identified.

4.4.2 On 6 February 2020, Dora's blood results showed an increased alanine transaminase (ALT) level (see section 2.1.16). While an indicator of paracetamol overdose, increased ALT can also be due to numerous other causes. A junior doctor reviewed the blood results and discussed them with a senior colleague. During this conversation, the senior suggested paracetamol overdose as a possible reason for the raised ALT and advised taking a further blood test to check Dora's paracetamol levels. In addition, they told the junior doctor to discontinue paracetamol while awaiting the results. From the evidence gathered by the

investigation, it appears that paracetamol overdose was thought to be one of a number of possibilities rather than a likely scenario requiring urgent action. The blood test was requested and taken on 7 February 2020 – 26 hours after Dora's last dose of paracetamol. The result came back the same day, and showed an abnormal paracetamol level of 42mg per litre.

4.4.3 Figure 4 shows the concentration of paracetamol on the vertical axis plotted against time (up to 24 hours from the last dose) on the horizontal axis. Patients whose paracetamol concentration is on or above the treatment line require treatment. The red dot shows Dora's paracetamol level; it is significantly above the line, indicating that she needed treatment.

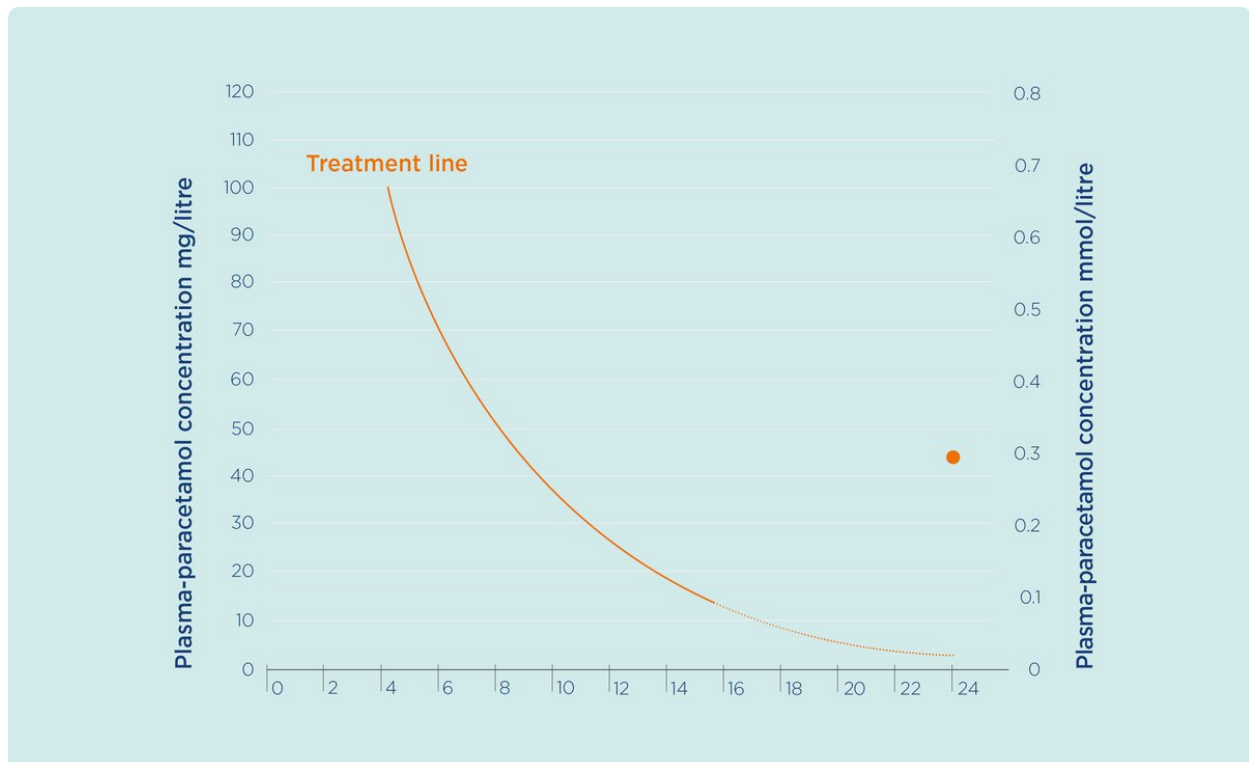


Figure 4 Paracetamol nomogram

Patients whose plasma-paracetamol concentrations are on or above the treatment line should be treated with acetylcysteine by intravenous infusion.

The prognostic accuracy after 15 hours is uncertain, but a plasma-paracetamol concentration on or above the treatment should be regarded as a serious risk of liver damage.

4.4.4 When the medical team reviewed the blood results showing the raised paracetamol level, Dora was prescribed N-acetyl cysteine – the antidote to paracetamol – to be given intravenously by nursing staff. This was prescribed at 11:10 hours on 7 February 2020 and administered approximately 10 hours later at 21:00 hours, 28 hours after a doctor had first queried paracetamol toxicity.

4.4.5 A contributory factor to this delay was that the ward team was unable to insert a cannula and so required help from the vascular access team. This team specialises in siting cannulas in patients for who, for various reasons, this is difficult to achieve. The vascular access nurse who saw Dora was also unable to insert a cannula. They escalated the matter to a vascular access doctor, who was able to insert the cannula at 18:30 hours. Following insertion of the cannula, the nurses identified that not all of the necessary details relating to N-acetyl cysteine administration had been written on the medication chart. The nursing team asked the ward doctor to amend the prescription. This doctor was responsible for 10–14 wards and was on another ward at the time of the request. It took approximately 2 hours for the prescription to be amended.

4.4.6 The investigation recognises that paracetamol overdose is usually seen and treatment initiated in the emergency/acute setting, following an accidental or intentional ingestion of a number of paracetamol tablets. The investigation was told that staff in the inpatient setting will be less familiar with the urgency for, and initiation of, treatment for paracetamol overdose.

Summary

4.4.7 There was a delay in initiating treatment once Dora's paracetamol overdose had been identified. This delay was contributed to by omissions in prescribing and difficulty in siting a cannula.

4.4.8 Staff in emergency and acute settings are more familiar with managing paracetamol overdose than those on a general medical ward.

5 Findings and analysis – the wider investigation

This section sets out the findings from the investigation's analysis of evidence in the context of the wider healthcare system.

The reference event involved a patient, Dora, who weighed less than 50kg on admission to hospital. She was weighed 12 days after her admission and found to weigh 40.5kg. During her stay in hospital, Dora was prescribed paracetamol at a dose of 1g four times a day. Liver function tests did not raise concerns until day 29 of Dora's admission. In the week prior to this, on all but one day, Dora received a maximum of 2g paracetamol per day. She subsequently developed liver toxicity.

The wider investigation gathered evidence regarding the reference event and developed safety recommendations.

The findings are presented within the following themes:

- Prescribing guidance for clinicians.
- Weighing patients in hospital.

5.1 Prescribing guidance for clinicians

5.1.1 Medicine manufacturers require a licence for the use of each medicine in the UK.

Licences are issued by the Medicines and Healthcare products Regulatory Agency (MHRA).

The MHRA is an arm's length body of the UK government's Department of Health and Social Care, and works on behalf of health ministers who act as the 'licensing authority'. The medication licence includes that medicine's indications for use, the dose to be taken and any restrictions to its use (for example, pregnancy or specific health conditions).

5.1.2 In addition to the medication licence, clinicians can obtain prescribing guidance from the British National Formulary (BNF) and clinical knowledge summaries (CKSs).

5.1.3 The BNF is a joint publication of the Royal Pharmaceutical Society and the British Medical Association. BNF content is available to the NHS through a contract with the National Institute for Health and Care Excellence (NICE); BNF content is available on the NICE website, within the BNF App and in print.

5.1.4 CKSs are developed by a commercial organisation called Clarity Informatics. Clarity Informatics is contracted by NICE to supply practical information for clinicians relating to common conditions managed in primary care. CKSs are published on the NICE website, and the information is publicly accessible.

5.1.5 At the time of the HSIB investigation, the information regarding the dose of oral paracetamol to be prescribed to patients who weigh less than 50kg differed between the BNF and CKS (see table 2).

Table 2 Guidance on oral paracetamol prescribing in adults

Dose	British National Formulary (Joint Formulary Committee, 2020)	Clinical Knowledge Summary (Clarity Informatics commissioned by the National Institute for Health and Care Excellence, 2020)
Adults	0.5–1g every 4–6 hours; max. 4g/day	0.5–1g every 4–6 hours as required; max. 4g/24 hours
Adults 40–49kg	Caution in patients with bodyweight under 50kg; use clinical judgement to adjust the dose	1g three times a day; max. 3g in 24 hours

Dose	British National Formulary (Joint Formulary Committee, 2020)	Clinical Knowledge Summary (Clarity Informatics commissioned by the National Institute for Health and Care Excellence, 2020)
Adults 33–39kg	Caution in patients with bodyweight under 50kg; use clinical judgement to adjust the dose	15mg/kg four times a day; max. 60mg/kg in 24 hours

5.1.6 Thus, in their 2020 guidance, CKS advised that a reduced paracetamol dose be given to patients weighing less than 50kg and recommended specific doses for patients weighing 33–39kg and 40–49kg (Clarity Informatics commissioned by the National Institute for Health and Care Excellence, 2020). Although the BNF does not recommend specific dose reductions, it does advise that clinical judgement should be used to adjust the dose of oral and intravenous (IV) paracetamol in patients at risk of experiencing toxicity at therapeutic doses, particularly those with bodyweight of less than 50kg and those with risk factors for hepatotoxicity (Joint Formulary Committee, 2020).

5.1.7 In November 2021, following HSIB's investigation, Clarity Informatics commissioned by the National Institute of Health and Care Excellence, further updated the CKS and removed the specific doses for patients weighing 33–39kg and 40–49kg, making the guidance more in line with information provided in the BNF and that published by the MHRA. The CKS now states: 'Use clinical judgement to adjust the dose of oral paracetamol in people with risk factors for hepatotoxicity, such as liver disease or body weight less than 50 kg.' If risk factors are present the guidance recommends 'Consider reducing the dose of paracetamol to a maximum of 3 g in 24 hours (for example 1 g three times daily) or use 15mg/kg every 4–6 hours (maximum of 60 mg/kg in 24 hours) as a guide.' (Clarity Informatics commissioned by the National Institute of Health and Care Excellence, 2021)

5.1.8 While the BNF does not state a specific reduced dose of oral paracetamol to be prescribed for adults who weigh less than 50kg, it does give a reduced dose for IV use in this population of 15mg/kg every 4–6 hours, with a maximum dose of 60mg/kg per day (Joint Formulary Committee, 2020), which reflects the Summary of Product Characteristics (Electronic medicines compendium, 2021).

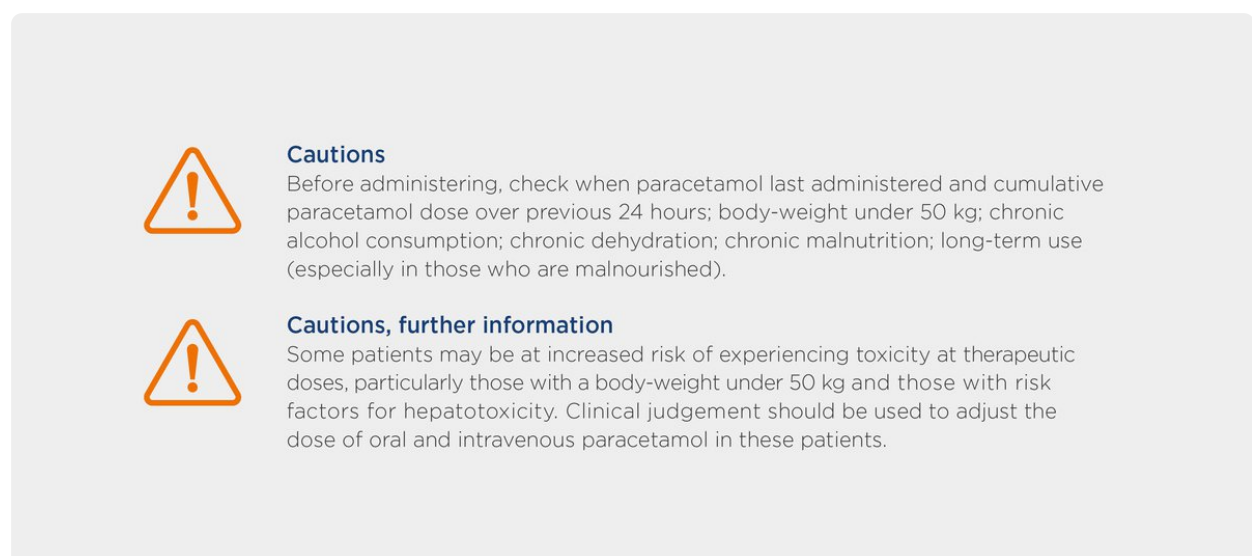
5.1.9 The investigation was told by multiple stakeholders that IV paracetamol is a much newer product than oral paracetamol. As a result, there were more extensive clinical trials providing data, which included weight-based dosing. This information is not available for oral paracetamol. To obtain such data, which would provide information about liver toxicity and low bodyweight, large-scale clinical trials would need to be undertaken. Given how well established and well tolerated paracetamol is, representatives from the BNF commented that such trials seemed unlikely to take place. Furthermore, the MHRA told the investigation that in the UK, any

medicines that are available to buy over the counter, such as oral paracetamol, cannot have dosage instructions that are dependent on an individual's weight. There are many practical reasons for this, one of which is that not everyone owns or is able to use a set of scales. Of note, and in recognition of these difficulties, children's paracetamol dosing is given by age and not weight.

5.1.10 In discussions with representatives from the BNF, it was highlighted that oral paracetamol is frequently prescribed and, as such, the oral doses are well known to clinicians. This may mean that clinicians are unlikely to refer to a reference source when prescribing this drug.

5.1.11 Representatives from the BNF told the investigation that any changes to dosing in the BNF would need to be informed by significant evidence-based information. They said they work closely with the MHRA and clinical experts in the field to ensure the BNF's content is up to date with the latest evidence.

5.1.12 Representatives from the BNF told the investigation that the recommendation for a 0.5–1g dose provided a range from within which they would expect a clinician to decide an appropriate dose. This decision would be informed by clinical factors. They noted that the BNF includes cautions with respect to prescribing paracetamol that highlight some of the clinical factors to be considered (see figure 5).



Cautions

Before administering, check when paracetamol last administered and cumulative paracetamol dose over previous 24 hours; body-weight under 50 kg; chronic alcohol consumption; chronic dehydration; chronic malnutrition; long-term use (especially in those who are malnourished).

Cautions, further information

Some patients may be at increased risk of experiencing toxicity at therapeutic doses, particularly those with a body-weight under 50 kg and those with risk factors for hepatotoxicity. Clinical judgement should be used to adjust the dose of oral and intravenous paracetamol in these patients.

Figure 5 Cautions in the British National Formulary with respect to the use of paracetamol in adults (Joint Formulary Committee, 2020)

5.1.13 The investigation sought evidence of the prevalence of significant harm caused by unintentional overdose of oral paracetamol in adult inpatients. The investigation reviewed two national data sources:

- The MHRA – adverse medication events can be reported via what is known as the ‘yellow card scheme’. The scheme is run by the MHRA and is the UK system for collecting and monitoring information on safety concerns, such as suspected side effects or adverse events involving medicines and medical devices. The scheme relies on voluntary reporting of suspected side effects or medical device incidents by health professionals and the public, including patients, carers and parents. Because reporting is voluntary, it may not accurately capture the number of unintentional overdoses.
- Strategic Executive Information System (StEIS) – all trusts in England are required to report serious incidents resulting in significant harm into this national database.

5.1.14 A review of the MHRA yellow card data identified 14 cases of liver toxicity in patients weighing between 14kg and 50kg from 1995 to 2021. A review of the cases did not specify any situations in which the patient was underweight and received oral paracetamol resulting in toxicity at 4g in 24 hours. Many of the cases related to self-administration at home and the administration of IV paracetamol, or the patient had other co-morbidities predisposing them to liver toxicity. This data reflects the fact that there is weak evidence to attribute paracetamol-induced liver toxicity to low bodyweight alone. The investigation was unable to obtain data on paracetamol usage; however, one stakeholder estimated that many hundreds of thousands of paracetamol doses are given in hospitals each year, and many millions of doses are taken in the community.

5.1.15 A review of incidents reported to StEIS between 1 April 2018 and 31 March 2021 (see Appendix 1) identified four cases of unintentional overdose of oral paracetamol in adult inpatients who weighed less than 50kg. In each of these incidents, the weight of the patient had not been documented and the patient was prescribed paracetamol at a dose of 1g four times a day.

5.1.16 The investigation was mindful that while paracetamol toxicity is highlighted in both the BNF and CKS as a risk for patients with low bodyweight, there are studies highlighting cases of toxicity in adults who weigh more than 50kg and have no other risk factors. In one study, which describes the case of two older patients who had no risk factors for paracetamol toxicity and had a bodyweight of more than 50kg. The patients developed paracetamol toxicity at the maximum dose of 1g four times a day (Ging et al, 2016).

5.1.17 Representatives from the BNF said they were aware of the reduced dosing recommended in the CKS. They noted that different bodies can review the same evidence, and yet arrive at differing conclusions for guidance. They said it would be beneficial for there to be

consistency across guidance and that this may be best achieved by the relevant bodies reaching a consensus. They thought there was the potential for such a consensus in relation to oral paracetamol.

5.1.18 The investigation interviewed the Medical Director at Clarity Informatics, who said they have editorial independence and that they cast a “wider net” than others when reviewing literature, which can result in variance in guidance. They said they “overcommunicate to give a broader view” with the aim of translating secondary care information to primary care practitioners. The CKS represents all the evidence when there are options for treatment. The Medical Director stated that the bioactivity of paracetamol is likely to be the same regardless of how it is administered (IV or oral). However, this view on bioactivity was not universal among stakeholders. The investigation was told by one stakeholder that the concentration of paracetamol reached was higher in IV administration than following an oral dose.

5.1.19 A representative from NICE told the investigation they would prefer a consistent message on paracetamol prescribing, but that they have to recognise the editorial independence of the commercial organisations that are contracted to provide information. They also said that any commercial organisation contracted by NICE to provide information to the NHS goes through a periodic accreditation process.

International context

5.1.20 In the USA, oral paracetamol is available as 325mg tablets to make products ‘safer for patients’ (US Food and Drug Administration, 2018). The dose recommendation for the public is one or two tablets four times a day, meaning that a person could take 2.6g rather than 4g in 24 hours, as in the UK. The US Food and Drug Administration, which performs a similar function to the UK’s MHRA, states that the reason for the dosing is to ‘help to reduce the risk of severe liver injury [...] associated with [paracetamol]’ (US Food and Drug Administration, 2018). Despite the availability in the USA of 325mg tablets, the advice for healthcare professionals, as in the UK, is for patients to take a maximum paracetamol dose of 4g in 24 hours (US Food and Drug Administration, 2018).

5.1.21 The investigation was told by the MHRA that some countries in the EU have a different recommendation for the maximum dosage of oral paracetamol. In the Netherlands, for example, the maximum daily dose of oral paracetamol for adults and children who weigh more than 55kg is 3g in 24 hours; the maximum daily dose for adults who weigh less than 50kg is 60mg/kg, not to exceed 2g (GlaxoSmithKline, 2016). The investigation noted that there is no guidance for adults who weigh 50–55kg. The MHRA said the recommendations in EU countries were based on adverse events (which may or may not be related to the medication) or adverse reactions (where a causal relationship between the drug and the side effect is suspected), rather than clinical trial information.

5.1.22 Representatives from the MHRA told the investigation that the MHRA had reviewed the recommended dosages from other countries and said that the UK licenced dose is in line with the available evidence. Furthermore, they said that having an oral tablet containing 325mg paracetamol could introduce the risk of calculation errors by healthcare professionals, patients and carers, with the potential for unintentional overdose.

Local guidance

5.1.23 The investigation found examples of trusts developing their own guidance for prescribing oral paracetamol to patients weighing less than 50kg. In one, which had an electronic prescribing and medication administration system, the system had been configured so that paracetamol prescribing was linked to the patient's weight. This meant that a patient who weighed 40–49kg could not be prescribed more than 3g paracetamol in 24 hours, and a patient who weighed less than 40kg could not be prescribed more than 500mg or 15mg/kg paracetamol four times a day.

5.1.24 The lack of evidence regarding the prescribing of oral paracetamol for adults with low bodyweight, coupled with inconsistent guidance between the BNF and CKS, may contribute to local variations in practice. The investigation considered that a consensus on this matter would promote standardisation and facilitate consistent practice.

HSIB makes the following safety observation

Safety observation O/2022/152:

It may be beneficial for the evidence on oral paracetamol and low bodyweight to be reviewed by the relevant national bodies to reach a consensus and agree standardised prescribing guidance.

5.2 Weighing patients in hospital

5.2.1 The investigation found that weighing a patient was often not perceived as a priority. Furthermore, as in the reference event, some staff said they believed that it is possible to estimate a patient's weight by visual assessment. Evidence has found that this is not a reliable way to establish the weight of a patient (Greene et al, 2004). For example, the President of the British Association of Parental and Enteral Nutrition (BAPEN) said that although there is a national policy and governance on weighing patients and nutritional management, challenges remain to their implementation in practice. They said that nutrition and a patient's weight can

often be viewed as “less important” than other aspects of clinical care, and can be seen as the responsibility of dietitians and nurses. The President stated that adequate nutrition (as reflected by a patient’s weight) plays an important role in recovery, especially in patients who are frail.

5.2.2 In addition to playing a role in a patient’s recovery, malnutrition is a risk factor for paracetamol-induced liver toxicity (see section 1.2.7). The Chair of the Clinical Standards Group at the National Poisons Information Service explained that this is because patients who are malnourished have a reduced amount of an antioxidant called glutathione. Glutathione helps to cleanse the liver of harmful substances, including products resulting from the breakdown of paracetamol. Patients who are malnourished may or may not be underweight. While this investigation focuses specifically on patients who are underweight, rather than those who are malnourished, Dora may have been at risk of liver toxicity for both reasons.

5.2.3 There is no national dataset to evidence the degree to which trusts are compliant with NICE guidance, which states patients should be weighed on admission and weekly thereafter (National Institute for Health and Care Excellence, 2017). BAPEN conducts a national audit on aspects of hospital inpatient nutrition (British Association of Parental and Enteral Nutrition, 2014). This includes documenting patients’ weight. However, the audit is directed at patients with identified nutritional needs who are, therefore, more likely to have their weight recorded. This audit data is therefore unreliable as a proxy measure for the number of patients in hospital who are weighed.

5.2.4 The investigation found examples of trusts that were exploring ways to ensure patients were weighed. One trust with an electronic prescribing and medication administration system told the investigation that it was considering “linking the weight of the patient with prescribing medications” so that prescribing could not happen without a patient’s weight being entered into the system.

5.2.5 The President of BAPEN told the investigation that the task of weighing patients needs to be made easier for staff if it is to be reliably undertaken. The investigation considered available technological solutions. For example, there are beds with built-in scales, which are most often used in intensive care units where patients are often immobile. The increased use of such beds would eliminate the time taken to weigh a patient and the need for multiple staff to undertake the task. Such solutions provide a system-focused intervention, which have been shown to be more effective than policy, guidance and training (see figure 3).

5.2.6 Beds with built-in scales are considerably more expensive than standard hospital beds. The investigation spoke with a company that supplies beds to NHS hospitals. The company told the investigation that a standard hospital bed costs around £6,000, while a bed with built-in scales (among other additional features) costs around £13,000–14,000. The company said that

hospitals tend to have no more than two or three of these beds. At more than double the cost of a standard bed, the widescale use of beds with built-in scales is unlikely given financial challenges of many NHS trusts.

5.2.7 The investigation was made aware of other technological options, including weigh bridges, which patients can be wheeled to on their bed. However, this requires a member of nursing staff and a porter, so is not without resource costs and logistical challenges.

5.2.8 Another option is bed-platform scales, which are essentially metal plates that can be inserted under each bed wheel to then weigh the bed and patient. This option negates the financial outlay of purchasing individual beds with integral weighing facilities.

HSIB makes the following safety observation

Safety observation O/2022/153:

It may be beneficial for available technological solutions, such as beds with built-in scales, to be used to weigh patients. However, the cost of such equipment makes its widespread adoption within the NHS challenging.

6 Summary of findings and safety observations

6.1 Findings

- Oral paracetamol is a widely used medication that has few side effects for most people.
- There is limited data on how oral paracetamol affects adults with low bodyweight.
- Although liver toxicity is a recognised risk with oral paracetamol, evidence regarding the relationship between low bodyweight and the risk of liver toxicity is unclear.
- Two independent bodies are contracted to provide oral paracetamol prescribing guidance for clinicians. The information provided is not consistent.
- There is potential for electronic prescribing and medication administration systems to prompt healthcare providers to record a patient's weight and consider liver toxicity in those who weigh less than 50kg.
- Environmental and other factors create challenges to the timely weighing of patients on a ward.

HSIB makes the following safety observations

Safety observation O/2022/151:

It may be beneficial for electronic prescribing and medication administration systems to include an alert for oral paracetamol that prompts documentation of a patient's weight and consideration of the risk of liver toxicity when their weight is less than 50kg.

Safety observation O/2022/152:

It may be beneficial for the evidence on oral paracetamol and low bodyweight to be reviewed by the relevant national bodies to reach a consensus and agree standardised prescribing guidance.

Safety observation O/2022/153:

It may be beneficial for available technological solutions, such as beds with built-in scales, to be used to weigh patients. However, the cost of such equipment makes its widespread adoption within the NHS challenging.

7 Appendix 1: Strategic Executive Information System search

Source data	Strategic Executive Information System
Date of extraction	13 July 2021
Date used for qualifying extraction	1 April 2018–31 March 2021
Categorical filters	Medication incident
Free-text terms	'Paracet' to account for spelling errors
Other notes	Manual review of incidents to identify if they met the criteria

- The initial search identified 1,908 incidents relating to medication.
- The free-text search identified 34 incidents containing the phrase 'paracet' (to account for spelling errors).
- A review of these 34 incidents found that 15 of the incidents related to unintentional paracetamol overdose, of which 11 occurred in an acute hospital.
 - Of those, four cases related to paediatric patients and were excluded from further review as this investigation focused on adults.

- Of the remaining seven cases, four related to adults with low bodyweight, two related to patients with known liver disease and one related to a woman who was 17 weeks pregnant.

8 References

Abdulla, A., Adams, N., Bone, M., Elliott, A. M., Gaffin, J., Jones, D., Knaggs, R., Martin, D., Sampson, L., Schofield, P. and British Geriatric Society. (2013) Guidance on the management of pain in older people. *Age and Ageing*, 42 (Suppl 1), i1-57.

Bataller, R. M. (2007) Evidence for practice: education about the dangers of acetaminophen. *Journal of Emergency Nursing*, 33, 327-330 [Online]. Available at <https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medc&AN=17643793> (Accessed 15 September 2020).

British Association of Parental and Enteral Nutrition. (2014) Nutrition screening surveys in hospitals in England, 2007–2011 [Online]. Available at <https://www.bapen.org.uk/pdfs/nsw/bapen-nsw-eng.pdf> (Accessed 19 November 2021).

British Liver Trust. (2017) Researchers shed new light on how paracetamol causes liver damage [Online]. Available at <https://britishlivertrust.org.uk/researchers-shed-new-light-paracetamol-causes-liver-damage/> (Accessed 17 August 2020).

Caparrotta, T. M., Antoine, D. J. and Dear, J. W. (2018) Are some people at increased risk of paracetamol-induced liver injury? *European Journal of Clinical Pharmacology*, 74(2), 147-160.

Carayon, P., Schoofs Hundt, A., Karsh, B. T., Gurses, A. P., Alvarado, C. J., Smith, M. and Flatley Brennan, P. (2006) Work system design for patient safety: the SEIPS model. *Quality & Safety in Health Care* 15 (Suppl. 1), i50-i58 [Online]. DOI: 10.1136/qshc.2005.015842.

Charpiat, B., Henry, A., Leboucher, G., Tod, M. and Allenet, B. (2012) Overdosed prescription of paracetamol (acetaminophen) in a teaching hospital. *Annales Pharmaceutiques Francaises*, 70(4), 213-218.

Claridge, L. C., Eksteen, B., Smith, A., Shah, T. and Holt, A. P. (2010) Acute liver failure after administration of paracetamol at the maximum recommended daily dose in adults. *British Medical Journal*, 341, c6764.

Clarity Informatics commissioned by the National Institute for Health and Care Excellence. (2020) Clinical Knowledge Summary. Analgesia – mild-to-moderate pain. Scenario: paracetamol [Online]. Available at <https://cks.nice.org.uk/topics/analgesia-mild-to-moderate-pain/management/paracetamol> (Accessed 10 September 2021) No longer available due to update.

Clarity Informatics commissioned by the National Institute for Health and Care Excellence. (2021) Clinical Knowledge Summary. Analgesia – mild-to-moderate pain. Scenario: paracetamol [Online]. Available at <https://cks.nice.org.uk/topics/analgesia-mild-to-moderate-pain/management/paracetamol> (Accessed 25 January 2022).

Dear, J. W., Antoine, D. J. and Park, B. K. (2015) Where are we now with paracetamol? British Medical Journal, 351, h3705.

Electronic medicines compendium (2021) Paracetamol 10 mg/ml solution for infusion [Online]. Available at <https://www.medicines.org.uk/emc/product/12744/smpc> (Accessed 21 January 2022).

Ganger, D. R., Rule, J., Rakela, J., Bass, N., Reuben, A., Stravitz, R. T., Sussman, N., Larson, A. M., James, L., Chiu, C., Lee, W. M. and Acute Liver Failure Study Group (2018) Acute Liver Failure of Indeterminate Etiology: A Comprehensive Systematic Approach by An Expert Committee to Establish Causality. American Journal of Gastroenterology, vol. 113, no. 9, p. 1319 [Online]. DOI: 10.1038/s41395-018-0160-2.

Ging, P., Mikulich, O. and O'Reilly, K. M. A. (2016) Unexpected paracetamol (acetaminophen) hepatotoxicity at standard dosage in two older patients: time to rethink 1 g four times daily? Age and Ageing, 45(4), 566-567.

GlaxoSmithKline. (2016) Panadol Gladde tablet, filmomhulde tabletten [Online] [In Dutch]. Available at <https://db.cbg-meb.nl/bijsluiters/h18550.pdf> (Accessed 21 January 2022).

Greene, S., Dargan, P., Shin, G. Y. and Jones, A. I. (2004) Doctors and nurses estimation of the weight of patients: a preventable source of systematic error. Journal of Toxicology, 42(5), 611-615.

Healthcare Safety Investigation Branch. (2020) The role of clinical pharmacy services in helping to identify and reduce high-risk prescribing errors in hospital [Online]. Available at <https://www.hsib.org.uk/investigations-and-reports/the-role-of-clinical-pharmacy-services-in-helping-to-identify-and-reduce-high-risk-prescribing-errors-in-hospital/> (Accessed 21 January 2022).

Holden, R. J., Carayon, P., Gurses, A. P., Hoonakker, P., Schoofs Hundt, A., Ant Ozok, A. and Rivera-Rodriguez, A. J. (2013) SEIPS 2.0: a human factors framework for studying and improving the work of healthcare professionals and patients. *Ergonomics*, 56 (11), 1669-1686.

Joint Formulary Committee. (2020) British national formulary. Paracetamol [Online]. Available at <https://bnf.nice.org.uk/drug/paracetamol.html> (Accessed 7 September 2020).

Khandelwal, N., James, L. P., Sanders, C., Larson, A. M., Lee, W. M. and Acute Liver Failure Study Group (2011) Unrecognized acetaminophen toxicity as a cause of indeterminate acute liver failure. *Hepatology*, vol. 53, no. 2, pp. 567–576 [Online]. DOI: 10.1002/hep.24060.

National Institute for Health and Care Excellence. (2017) Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition. Clinical guideline [CG32] [Online]. Available at <https://www.nice.org.uk/guidance/cg32> (Accessed 10 September 2021).

National Poisons Information Service. (n.d.) Toxbase [Online]. Available at <https://www.toxbase.org> (Accessed 19 October 2020).

NHS Improvement. (2017) Patient safety review and response report: April to September 2016 [Online]. Available at <https://www.england.nhs.uk/wp-content/uploads/2021/02/ps-review-and-response-report-april-sept-2016.pdf> (Accessed 25 September 2020).

Niedrig, D. F., Bucklar, G., Fetzer, M., Mächler, S., Gött, C., & Russmann, S. (2016) Paracetamol overdosing in a tertiary care hospital: implementation and outcome analysis of a preventive alert programme. *Journal of Clinical Pharmacy and Therapeutics*, 41 (5), 515-518.

Pearce, B. and Grant, I. S. (2008) Acute liver failure following therapeutic paracetamol administration in patients with muscular dystrophies. *Anaesthesia*, 63 (1), 89-91.

Prescott, L. F. (2000) Paracetamol: past, present, and future. *American Journal of Therapeutics*, 7 (2), 143-147.

Rasmussen, J. (1997) Risk management in a dynamic society: a modelling problem. *Safety Science*, 27 (2-3), 183-213.

Rotundo, L. and Prysopoulos, N. (2020) Liver injury induced by paracetamol and challenges associated with intentional and unintentional use. *World Journal of Hepatology*, 12 (4), 125-136 [Online]. Available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7336293> (Accessed 14 September 2021).

Royal College of Obstetricians and Gynaecologists (2015) Each Baby Counts full report 2015. Available at <https://www.rcog.org.uk/globalassets/documents/guidelines/research--audit/each-baby-counts-2015-full-report.pdf> (Accessed 14 January 2022).

US Food and Drug Administration (2018) FDA drug safety communication: prescription acetaminophen products to be limited to 325 mg per dosage unit; boxed warning will highlight potential for severe liver failure [Online]. Available at <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-prescription-acetaminophen-products-be-limited-325-mg-dosage-unit> (Accessed 10 September 2021).

Watkins, P. B., Kaplowitz, N., Slattery, J. T., Colonese, C. R., Colucci, S. V., Stewart, P. W. and Harris, S. C. (2006) Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: a randomized controlled trial. JAMA, 296 (1), 87-93.

Weiler, S., Bellmann, R., & Kullak-Ublick, G. A. (2015) [5-Oxoproline (pyroglutamic acid) acidosis and acetaminophen – a differential diagnosis in high anion gap metabolic acidosis] [In German]. Therapeutische Umschau, 72 (11-12), 737-741.

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