Iron overdose epidemiology, clinical features and iron concentration-effect relationships: the UK experience 2008–2017

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Abstract

Background: Iron poisoning is potentially serious, but mortality has fallen worldwide since implementation of pack size and packaging restrictions, and changes in iron use during pregnancy. The management of individual cases of overdose remains problematic due to uncertainty about indications for antidote. We examine the epidemiology of iron overdose in hospital cases referred to the UK National Poisons Information Service (NPIS) and evaluate the toxicokinetics of iron in patients ingesting only iron preparations.

Methods: Anonymized hospital referral patient data from the NPIS database were collated for the period 1 January 2008 to 31 July 2017. Information was extracted, where recorded, on type of ingestion [iron alone (single), or combined with other agents (mixed)], reported dose, iron salt, timed iron concentrations and symptoms. In single-agent ingestions, the relationships between reported elemental iron dose, early concentrations (4–6 h), and symptoms were evaluated in teenagers and adults (≥13 years) and children (<12 years) using standard statistical techniques (correlation and unpaired nonparametric comparisons). In those patients with sufficient sample points (three or more), a simple kinetic analysis was conducted.

Results: Of 2708 patients with iron overdoses referred by UK hospitals for advice during the 9.7 years study period, 1839 were single-agent ingestions. There were two peaks in age incidence in single-agent exposures: 539/1839 (28.4%) were <6 years (54.1% males) while 675/1839 (36.7%) were between 13 and 20 years (91% females), the latter a substantial excess over the proportion in the totality of hospital referrals to the NPIS in the same period (13–20 years: 23,776/144,268 16.5%; 67.5% female) (p < .0001 overall and for female %). In 475 teenagers and adults and 86 children, with at least one-timed iron concentration available, there was no correlation between stated dose and iron concentration measured 4–6 h post-ingestion. Observed peak iron concentrations were not related to reported symptoms in adults. Initial iron concentrations were significantly higher in 30 patients (25 adults, 5 children) who received desferrioxamine (DFO) compared to those that did not (no DFO: mean 63.8 μmol/L (95% CI 69.2–87.7), median 78.1; Mann–Whitney p < .0018). No significant differences in symptoms were observed pre-treatment between DFO-treated and untreated groups. No patients died in this cohort.

Conclusion: Single-agent iron exposures reported from UK hospitals were most common in children <5 years and young people aged 13–20 years. Poisoning with organ failure was not identified and there were no fatalities. No correlations were observed between reported iron doses and early concentrations, or between iron concentrations and symptoms in this cohort of mild-to-moderate poisoning.

Introduction

Iron overdose has the potential to cause dose-related major organ (especially liver) injury and death [1,2]. As recently as the 1990s, a case series suggested adult mortality in a Canadian hospital of 10% [3]. However, the epidemiology of iron poisoning has been changed since then by three key factors: a reduction in pack size; the increased use of child-resistant containers [4]; and reductions in the use of iron during pregnancy [5], reducing the quantity available in the community. The net effect in UK has been a reduction in severity of iron overdose, with the current mortality in UK (pop 53.1 million) being less than one per annum for the past decade (personal communication, UK Office of National Statistics, April 2017) and similar effects are seen elsewhere, as shown by recent US poison data [6].

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Supplemental data for this article can be accessed here.
The management of iron poisoning in the UK is with supportive care and the antidote deferoxamine (DEF), which is given according to symptoms and serum iron concentrations [7]. DFO is generally recommended for all patients with severe clinical features (e.g., reduced level of consciousness, shock, metabolic acidosis, convulsions, gastrointestinal hemorrhage, hemolysis) as well as symptomatic patients with iron concentrations >90 μmol/L (5 mg/L, 50 μg/dl), and considered in those with concentrations >55 μmol/L (3 mg/L, 300 μg/dl) and increasing (normal ranges: adult males: 10–32 μmol/L; 0.6–1.7 mg/L; 60–170 μg/dl; females 8.5–32 μmol/L; 0.50–1.65 mg/L; 60–165 μg/dl; children 8.5–24 μmol/L; 0.50–1.20 mg/L; 50–120 μg/dl). This advice is based on case series collected in the 1960s–1980s in North America, prior to reductions in availability of medicinal iron [8,9]. There are no previous published detailed epidemiologic data on iron poisoning in UK and no recent similar international studies.

The recommended intravenous DFO infusion rate is 15 mg/kg/h, to a maximum dose of 80 mg/kg over 24 h. This regimen is unlikely to bind clinically significant amounts of elemental iron in severe overdose, leading to uncertainty about efficacy [10]. Higher infusion rates have, however, been associated with adverse effects, especially the development of pulmonary edema [11], although the risk of this is not well defined.

The objectives of this study were to evaluate the current epidemiology of iron overdose in hospital admissions reported to the UK NPIS in telephone enquiries, and to explore the relationships between reported ingested dose, early (4–6 h) serum iron concentrations and development of toxic features in those with single-agent ingestions of iron.

Methods

Routine records of calls to the UK National Poisons Information Service (NPIS) are collected onto a common database, the UK Poisons Information Database (UKPID). This investigation focused on all records in which an iron preparation had been ingested in overdose was reported from a UK hospital for the period 1 January 2008 to 31 July 2017 (9 years 7 months). All identified case records were anonymized and then examined to identify those in which iron had been ingested alone (single agent), or in combination with other agents (mixed). In those who had ingested a single preparation overdose information extracted included age, sex, iron salt and preparation involved, patient weight, reported dose ingested, reported clinical features, total serum iron concentration(s) and time(s) of sample(s) post ingestion, prior to any administration of DFO. The elemental iron dose per kilogram body weight was calculated when adequate data were available. Reported symptoms used in the assessment of severity were vomiting, hematemesis, acidosis, decreased Glasgow Coma Scale (GCS) (GCS 5–14), coma (GCS <5) and hypotension, all as reported by the treating clinician. These were categorized as present or absent, so that associations between iron concentrations and symptoms could be examined.

For cases pre-February 2013 data were retrospectively extracted from routine call sheets as available. For the period after 2 February 2013, a prospective audit of all iron cases referred to the NPIS was conducted, with increased follow-up to try to ensure the full study data set was entered into the main call record.

For basic toxicokinetic assessments, timed sequential iron concentrations were recorded when available, prior to any administration of DFO. No systematic data on clinical responses after use of DFO were available, but no adverse responses to the antidote were reported to the NPIS. Age ranges for analysis were chosen to reflect the epidemiology observed, with a clear age division in overdoses seen between younger children and teenagers. The relationship between dose and concentration in teenagers and adults (≥13 years) and children (≤12 years) was therefore explored by examining data from patients in whom an iron concentration was recorded between 4 and 6 h post-ingestion, as iron concentrations generally peaked in this time frame in this series (Figures 3 and 4) and clinical decisions on management are often made in response to these early measurements. In the event of patients having more than one sample in this time frame, the highest value was used. The effect of initial iron concentrations on symptoms used when considering early use of DFO in the UK was examined by comparing concentrations in those with and without symptoms.

A basic kinetic analysis was done using data from those patients with at least three timed iron concentrations. Serum iron half-lives were calculated using regression analysis on log-transformed concentrations in patients with at least two further samples after the observed peak concentration, assuming log-linear kinetics and using a single compartment model. A more detailed analysis of iron pharmacokinetics is not possible with this type of data set as iron is an endogenous compound, with complex metabolism [12,13], and we have no data on baseline concentrations pre-overdose. Additionally, free iron, transferrin and ferritin concentrations are not routinely measured in the assessment of iron poisoning in the UK, preventing a full analysis.

Exploratory statistical analysis was performed using simple linear correlation (dose/concentration relationships) and Mann-Whitney tests for analyses involving concentrations and symptoms, or between those receiving or not receiving DFO.

This study did not require approval by a UK Research Ethics Committee as the UK Health Research Authority has declared that ethical approval is not needed for research studies that use information collected routinely by any UK administration (England, Wales, Scotland and Northern Ireland) as part of usual clinical care, provided this information is passed to the researchers in a fully anonymized format.

Results

Epidemiology of iron ingestions

A total of 2708 patients with iron overdoses were referred to the NPIS by UK hospital staff for advice in the study period, of which 1839 (~16/month) were ingestions of iron-containing medication alone (single-agent exposure).
Six hundred and thirty-eight of the cohort were children (≤12 years) of whom 586 were single ingestions; 2000 were teenagers and adults (≥13 years) (1198 single) and 65 were of unknown age (55 single).

Iron poisoning, either as single agent or as a mixed overdose, commonly involved children <6 years and teenagers, with peak incidence in those aged 2–3 years and 15 years of age; in single-agent ingestions 539 (28.4%) were <6 years (males 54.1%) and 675 (36.7%) were between 13 and 20 years of age (91% females). The great majority (70.1%) of those affected ≥13 years were females (Figure 1, Table 1, Supplementary Table S1). This contrasts with the profile of overall hospital telephone referrals to the NPIS in the period of this study, in which only 16.5% were aged 13–20 years, of which 67.5% were female (p < .0001 for proportions of overall cases aged 13–20 years and % female compared with iron) (Table 1). These data therefore show that iron poisoning is more frequently encountered in young adults than the generality of overdoses.

In single-agent ingestions, where recorded, the median reported dose of elemental iron ingested in adults was 1.95 g [interquartile range (IQR) 1.12–3.25] and the median dose/kg was 30.4 mg/kg (19.0–53.2). The median serum concentration at 4–6 h was 65.8 μmol/L (56.2–77.3). In children, the median dose ingested was 0.59 g (0.32–0.96) or 34.7 mg/kg (23–71.2), and median serum concentration at 4–6 h was 66 μmol/L (56.2–77.0).

Toxicokinetic sample set

Concentration–time relationships

The pattern of ingested iron salts was examined in adults and children. We then analyzed the relationship between ingested dose and peak (4–6 h) serum concentration of iron at peak (4–6 h) as suggested by the pattern in maximal concentrations observed and reported below. In those with multiple (two or more post-peak samples) we calculated apparent serum half-lives for iron.

Figure 1. Distribution of ages of hospital patients with iron overdose, highlighting age and sex patterns in those up to 45 years. Upper panel single ingestions, lower panel patients with iron in mixed ingestions. Rates per annum continued to slowly decline after 45 years in both groups (see also Table 1 and Supplementary Figure S1).
Data were available for toxicokinetic analysis for 475 teenagers and adults, and 86 children (≤12 years) who were reported to have ingested standard release products. The most frequently reported iron salt to be ingested in the kinetic data set was ferrous sulfate (65.4%), with ferrous fumarate (29%) being less common and gluconate (1.6%) rare. All of these patients had at least one timed sample; 182 adults and 35 children had two-timed samples; and 44 adults and 6 children ≤12 years had at least three-timed samples. We identified three individuals ingesting modified-release products, and they were not included in this analysis. In adults, while the doses/kg ingested were different between the two major salts [sulfate (mg/kg): mean 36.7 (95% CI 32.8–41.2), median 31.1; fumarate: mean 49.2 (41.2–57.2), median 34.0; p < .0326], the measured concentrations 4–6 h after ingestion were similar [sulfate (μmol/L): mean 68.0 (95% CI 66.2–71.8), median 66.0; fumarate: mean 66.0 (62.6–69.4), median 66.6; p = .347]. These data in adults suggest that bioavailability of fumarate and sulfate salts may be different in overdose. Numbers of each salt in children were much smaller and no differences were apparent. There were insufficient numbers of fumarate (5) and sodium federate (3) in adults to allow detailed analysis of these salts. In the remainder of cases, the salt ingested was not recorded.

In adults, the mean time after iron ingestion of the earliest sample collected was 5.8 h (95% CI 5.4–6.1, median 4.0) and the mean concentration at this time was 64.7 μmol/L (95% CI 63.0–66.4, median 64.4). In 41/182 (22.5%) patients with two or more timed concentrations, the second concentration exceeded the first, but in only one case was this increase clinically important (from 18 μmol/L at 1.5 h to 73 μmol/L at 7 h post-overdose, in a patient with vomiting). In other cases, any increases were by <15% of the initial concentration. There was no correlation between either reported total or weight corrected elemental iron dose ingested and concentration measured between 4 and 6 h post-overdose (Figure 2 and Supplementary Figure S1).

In children, the earliest concentration measurement in those with more than one blood sample available was always higher than in subsequent samples. The mean time of this sample was 4.1 h (95% CI 3.8–4.3; median 4.0) and mean concentration 67.3 μmol/L (95% CI 58.3–76.3; median 68).

Data on those patients with two or more samples have been plotted to show the time–concentration relationships in adults (Figure 3), and children (Figure 4). These plots illustrate that, following peak concentrations, iron concentrations fell slowly. Quantification of the rates of decline was done by calculating half-lives in those patients who had at least two further concentrations post-peak, in the absence of DFO.
treatment. In this cohort of 27 adult patients, the apparent mean half-life of iron concentration decline was 34.5 h (95% CI 22.2–46.8; median 20.9). In five children, where sufficient data were available, the apparent half-life was highly variable; individual values were 18.4, 19.0, 19.6, 60.7 and 79.2 h.

**Dose and concentration and symptoms**

The frequency of symptoms used routinely in clinical assessment of adults and children, vomiting, hematemesis, acidosis, hypotension and reduced GCS, were evaluated in patients using both initial concentration and dose, where available (474 aged ≥13 years; 86 children ≤12 years). The most frequent clinician-reported clinical feature was vomiting (28.9% adults and 20% children), followed by acidosis (5.9% adult and 8% children), with other features being less frequent (Table 2: adults; Table 3: children). No adult cases were reported with a GCS of ≥10.

In a multiple regression analysis, there was no significant effect of iron salt on frequency of any symptom of interest, whether expressed as total elemental iron or elemental iron/kg body weight. For simplicity, the median iron concentrations in patients with and without symptoms of interest are shown in Tables 2 (adults) and 3 (children). Although iron concentrations were higher in adults with vomiting, acidosis or decreased GCS, these differences were not statistically significant. The two children with decreased GCS had serum iron concentrations of 96 and 157 μmol/L at 6 and 2 h post-overdose respectively, but numbers were too small for standard non-parametric testing. Only one child had hypotension (concentration 79.8 μmol/L at 4 h).

**Use of DFO**

There were 25 adult patients and five children (all ≤2 years) in this cohort who were given DFO. No other chelation agents were administered. In 19 adults, DFO was given after the first iron sample had been obtained, in five after a second sample, and in one after the third sample (9 h post-overdose). The times of the first samples obtained, and mean concentrations at that time, were 6.04 h (95% CI 5.42–6.65, median 4) and 63.8 μmol/L (95% CI 62.1–65.6, median 64) in those not receiving DFO and 5.7 h (95% CI 4.07–7.33, median 4) and 78.5 μmol/L (95% CI 69.2–87.7, median 78.1) in those who did. There was no statistical difference in the timings of these samples, but the iron concentration was significantly greater in those adults receiving DFO ($p = .0018$, Mann–Whitney).

This difference was not found in children, likely due to the small sample size (no DFO: time 4.77 h (95% CI 4.10–5.45), median 4; concentration 64.8 μmol/L (95% CI 59.78–69.84), median 66.5. DFO: time 3.2 h (95% CI 1.84–4.56), median 4; mean concentration 80.3 μmol/L (95% CI 60.96–99.68), median 82) (Mann–Whitney for concentration, $p = .078$).

Age and symptom frequency were not significantly different between DFO and non-DFO groups in either adults or children.
Discussion

These data represent a large modern experience of iron poisoning, with 1819 single ingestion cases, of whom 28.5% were <6 years of age. Detailed data for this analysis were available for 475 (83%) adults aged ≥13 years, and 86 (15%) children aged ≤12 years, although relatively few patients were symptomatic. Overall, only 6.5% received the antidote DFO and no deaths were reported due to iron. There are unfortunately no previous series of this type published from UK to allow a historic comparison, but these cases appear less severe than some previous cohorts published from other countries [3,9]. They also resemble recent North American experience [6].

The first important finding from this research was the lack of a proportional increase in serum iron concentrations in the 4–6 h time-frame according to the reported dose of iron, expressed either as total dose or as dose/kg (Figures 2 and 3). This finding is, at first sight, surprising, but suggests that limited iron absorption may be a major factor in determining the initial peak serum concentration as seen in therapeutic doses peak concentrations, where peak concentrations occur within 4 h of ingestion but then fall rapidly as iron is redistributed [13]. Our findings are compatible with the kinetics of iron absorption being non-linear in overdose, as they are at therapeutic doses up to 100 mg, and that rate-limited absorption is present at moderate overdose, as it is at therapeutic concentrations [13–15].

Serial samples from patients showed a uniform pattern of blood concentrations, with slow post-peak reductions in total iron concentration. This may reflect continuing absorption, slow clearance, or both. The absorption of iron is normally by active transport [13–15]. It has been assumed that in large iron ingestions this process is overwhelmed and that iron is absorbed by passive diffusion [15]. The current data set would suggest that, in the dose ranges seen in this study passive diffusion does not occur. These data also show that in mild-to-moderate overdose major increases in iron concentrations were not seen more than 6 h post-ingestion.

A second finding to highlight was the absence of a clear relationship between initial iron concentrations and symptoms in adults. Features such as acidosis and coma are generally seen later in the course of toxicity in severe poisoning,
Figure 4. Timed elemental iron concentrations (\(\mu\text{mol/L}\)) in 35 children (\(\leq 12\) years) following iron overdose in patients who had two or more timed samples available. Top panel to 20 h lower to 9 h post-ingestion for purposes of clarity.

### Table 2. Data on initial iron concentrations (\(\mu\text{mol/L}\)) and presence or absence of symptoms in 474 adults (\(\geq 13\) years).

| Feature      | Present | Absent |
|--------------|---------|--------|
|              | \(N (\%)\) | Median Fe conc. (\(\mu\text{mol/L}\)) | 95% CI | \(N (\%)\) | Median Fe conc. (\(\mu\text{mol/L}\)) | 95% CI |
| Vomiting     | 137 (28.9) | 66.1 | 63.5–70.6 | 337 (71.1) | 64.0 | 61.8–65.7 |
| Hematemesis  | 11 (2.3) | 61  | 48.4–72.3 | 463 (97.7) | 64.4 | 63.0–66.6 |
| Acidosis     | 28 (5.9) | 68.5 | 62.5–75.3 | 446 (94.1) | 66.2 | 62.6–66.2 |
| Decreased GCS | 9 (1.9) | 67  | 56.7–90.8 | 465 (98.1) | 64.3 | 62.8–66.3 |
| Hypotension  | 9 (1.9) | 74  | 57.2–86.3 | 465 (98.1) | 64.4 | 62.8–66.3 |

None reached statistical significance.

### Table 3. Initial iron concentrations (\(\mu\text{mol/L}\)) and symptoms in 86 children (\(\leq 12\) years).

| Feature      | Present | Absent |
|--------------|---------|--------|
|              | \(N (\%)\) | Median Fe conc. (\(\mu\text{mol/L}\)) | 95% CI | \(N (\%)\) | Median Fe conc. (\(\mu\text{mol/L}\)) | 95% CI |
| Vomiting     | 20 (23.3) | 70  | 61.3–84.9 | 66 (76.7) | 65.5 | 57.9–68.1 |
| Hematemesis  | 4 (4.7) | 72.8 | 3.3–167 | 82 (95.3) | 67  | 60.2–69.1 |
| Acidosis     | 7 (8.1) | 70.6 | 52.8–95.2 | 79 (91.9) | 66  | 59.8–69.9 |
| Decreased GCS | 2 (2.3) | 126.5 \(^b\) | – | 86 (97.7) | 66.5 | 59.8–68.5 |

Only one child had hypotension.

\(^a\)Decreased GCS in two children with initial recorded concentrations of 96 and 157 \(\mu\text{mol/L}\). \(^b\)95% CI not calculated.
and generally thought to result from hepatic injury. No such cases were seen in adults in the present series. Nevertheless, if appearing early, these symptoms cause concern to treating clinicians, as they are often thought to indicate severe toxicity. This study therefore indicates a lack of utility of initial clinical features, whether toxicologically more likely early, such as nausea and vomiting, or later, such as acidosis and coma, in the assessment of patients at presentation.

In children, two cases of reduced GCS occurred in patients with initial iron concentrations of 96 and 157 \( \mu \text{mol/L} \) at 6 and 2 h post-overdose, respectively. Neither received DFO, and neither appeared to suffer organ damage. Two other children with concentrations above 100 \( \mu \text{mol/L} \) were conscious. These findings indicate that use of early CNS symptoms as a surrogate for systemic toxicity may be flawed in children with concentrations in the range seen in this study. Our findings extend those noted by Chyka et al. [16,17] in children 20 years ago. It is important to note that only three adult patients had concentrations above 110 \( \mu \text{mol/L} \), the highest being 157 \( \mu \text{mol/L} \). The latter was in a sample taken within 1 h of ingestion, and therefore not representative of most patients seen, in whom samples were taken later. Thus, these conclusions may not apply to very high iron ingestions, but the findings would apply to the vast majority of overdoses now seen in our practice.

Although these toxicokinetic and toxicodynamic data represent a large UK experience, they exclude patients treated with DFO by referring physicians at an early stage, prior to iron samples being obtained. This is because UK clinical laboratories do not differentiate iron bound to DFO from that not bound.

A small number of adults (25; 5.3%) and children (5; 5.8%) were given DFO following discussion with NPIS. Decisions on DFO were made by both NPIS and local clinicians, based on their experience, time after overdose, blood concentrations and symptoms. In adults, those given DFO had higher initial mean iron concentrations (77.7 versus 64.0 \( \mu \text{mol/L} \)) but in other respects were similar to those untreated. There was no clear difference in rate of DFO use by the different NPIS clinicians involved, most of whom advised DFO in at least one case. The overall favorable outcomes in this cohort in which, overall, very few received DFO, raise questions about efficacy and appropriate clinical criteria for use, which this study cannot answer. The small number of cases who die also means that it will be extremely difficult to obtain better information on DFO effectiveness in the UK.

**Limitations**

This study is based on reports to, and discussions with, poisons information center staff. It is therefore subject to potential confounders relating to “second hand” data. For example, we were unable to obtain detailed histories of precise iron preparation ingested in all cases. Many patients had only one iron sample, and few had the three or more samples necessary for a formal kinetic study. Furthermore, there was no information available on ferritin concentrations or free and bound iron, which may potentially affect our conclusions. This lack of data also mitigates against a full detailed kinetic analysis. It is possible some symptoms were also not reported after the initial call, although all cases were subject to follow-up. Precise details of acid base balance were not available, and we used the surrogate of “clinician reported acidosis”. This mitigates against optimal assessment of this potential marker of toxicity.

We were only able to study in detail about 21% of the total patients in the cohort discussed with NPIS, due to non-availability of the details required in this analysis in the remainder. However, in a subset of this cohort examined in the 3 years between 2014 and 2106, symptoms and/or dose ingested in those who received DFO without serum iron concentrations, and thus not included in this study, were not indicative of life-threatening ingestion [18]. We therefore consider it unlikely that we have missed important data that could alter our analysis or conclusion.

Overall these limitations seem therefore unlikely, in our view, to impact our key findings.

**Conclusion**

These findings demonstrate that while iron overdose continues to be reported to UK poisons centers, most cases do not involve substantial elemental iron doses, severe clinical features are uncommon, and death is extremely rare. These findings seem consistent with findings now reported on iron overdose elsewhere [6]. Young children constitute an important proportion of cases, despite regulatory attempts to limit access to iron in this age group. The results also suggest that at moderate overdose, iron absorption is dose-limited, with implications for clinical management and use of DFO, which is unnecessary in most ingestions now seen in UK.

Finally, in this population of moderate overdoses, with few symptomatic patients after single-agent iron ingestion, there was a lack of correlation between dose, concentration and clinical symptoms, apart perhaps for coma in children. This suggests that use of reported dose or serum concentration for predicting symptoms, and, conversely, symptoms for suggesting likely dose, are both unreliable in this patient group. Use of DFO appears to have likely been unnecessary in many, if not all patients bearing in mind the close similarity between treated and untreated groups and lack of poor outcomes reported to us. The use of DFO seems to be driven by a concern about potential hazards of iron derived from experience in older cohorts when larger iron doses were ingested. There seems a need to revisit the indications for DFO, as it would appear to be overused based on this experience.

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