ARxCH
Annual Review of Changes in Healthcare

Review of Iron-Overdose in Pediatric Patients

Emily Doycich, PharmD Candidate 2018[1]
Jason Guy, PharmD[1]
[1]*University of Findlay College of Pharmacy*

Abstract

The occurrence of iron overdose in children remains a prevalent occurrence in the United States despite efforts to combat this issue. This review discusses the mechanism behind iron poisoning, the presentation of toxic effects, and available treatment options after a potential poisoning has occurred. Keeping this information in mind when discussing iron-therapy with patients who have children at home is important. Parents and guardians of children should be made aware to contact poison control, 911, or bring their child to the nearest hospital.

The candy-like appearance of many medications can look desirable to children and have them confused as to the serious implications that may occur after ingestion. Specifically, the appearance of iron supplements has led to many cases of iron poisoning in children as these pills are typically sugarcoated and brightly colored.[1] There is also an assumed low-risk to iron-containing products, such as multivitamins, that may lead to less restricted access to these medications.[1] Iron over-dose is one of the leading causes of death in children under six years old, with approximately seventy-five percent of all iron overdose cases in 2014 being in children younger than six years old.[2] The risk of death from iron overdose in pediatric patients is ranked as high as other agents like cocaine, anticonvulsants, and antidepressants.[3] As health care professionals, it is important to have an awareness of prevalent adverse outcomes in the community. Using this knowledge, key preventative measures can be included along with medication counseling points to help in decreasing overdose situations. When ingested, iron is stored in a protein called ferritin, which is primarily found in tissue of the liver and heart.[4] The mechanisms of iron poisoning come into play after the iron-binding protein, ferritin, becomes saturated.[4] Even after there are no available proteins for binding, iron still is directed to the liver and heart and as a result, damage to these organs is seen early on in an overdose situation.[4] Several mechanisms are suggested as to how excess free iron may cause damage to the body. In the acidic environment of the stomach iron can cause direct irritation.[4] As iron travels through the gastrointestinal tract it becomes insoluble, forming complexes that lead to mucosal damage.[4] Free iron that passes across the cellular membrane concentrates in the mitochondria and draws electrons from entering the electron transport train.[4] Due to this, there is an increase in anaerobic metabolism, creating lactic acid and contributing to metabolic acidosis.[4] Free iron may lead to a decrease in coagulation not only through its damage to the liver but also through a possible impact on serine proteases.[4] In addition, free radicals are formed through reduction-oxidation reaction of free iron.[4] Free radicals are responsible for peroxidation of lipids and proteins, which then leads to damage of the effected organs.[4] Histamine and serotonin are released as a result of free iron.[4] The release of these neurotransmitters negatively affects the vascular system resulting in a decreased blood volume and, therefore, reduced cardiac output.[4]

Presentation of iron toxicity occurs in four stages. The first stage takes place from 30 minutes to 12 hours after ingestion.[5] Symptoms include vomiting, bloody diarrhea, abdominal pain, fever, and fatigue as a result of damage to the gastrointestinal tract.[5] Symptoms as a result of damage to other organs such as the central nervous system, cardiovascular system, pancreas, and liver may also present in this phase after more severe toxicity.[5] Usually no symptoms present during stage two (8-36 hours after ingestion) as a result of iron redistribution from the serum into intracellular compartments.[5] This time may be mistaken for resolution of symptoms after mild toxicity and patients should continue to be monitored.[5] During stage three liver injury/failure takes place.[5] Patients may

experience hypoglycemia, metabolic acidosis, cardiovascular collapse, shock, bleeding, coma, or seizures.[5] It is important to note that serum iron may not appear to be in a toxic range as free iron in the serum has been redistributed into intracellular compartments. Stage three lasts from 12-48 hours after ingestion of iron products.[5] During the final stage, 2-8 weeks after ingestion, a bowel obstruction, vomiting, or CNS effects may occur due to intestinal, pyloric, and antral stenosis.[5] Monitoring should include serum iron, total iron binding capacity, complete blood count, basic metabolic panel, and abdominal X-Ray within 6 hours of ingestion.[5]

Common iron containing medications (elemental iron) include ferrous gluconate (38mg), ferrous sulfate (65mg), ferrous fumarate (106mg), prenatal vitamins (~65mg), and multivitamins (~15mg).[6] When elemental iron concentrations surpass 60mg/kg in pediatric patients, serious adverse events and death may be experienced.[6] With this in mind, if more than 40mg/kg of elemental iron is ingested the pediatric patient should be taken to the emergency room for evaluation.[6] Treatment for iron toxicity includes several different options. If the abdominal x-ray shows non-dissolved tablets in the system then either whole bowel irrigation, gastric lavage, or endoscopic removal can be initiated.[7] These options will remove the iron containing products from the body, decreasing the amount of iron that can be absorbed into the body. Whole bowel irrigation is preferred when large quantities of iron-containing pills have been ingested.[7] If iron has made its way into the blood stream already, treatment depends on the free iron serum level. It is important to note that time since ingestion plays a role in interpretation of serum iron levels. When serum iron levels are under 55 μmol/L, no treatment is needed.[7] Serum iron levels between 55-90 μmol/L require observation.[7] With iron levels in this range it may be unknown whether iron is leaving the body or being redistributed into intracellular space. If no symptoms present then no treatment is needed.[7] Levels greater than 90 μmol/L require treatment with intravenous deferoxamine.[7] This agent will chelate with free iron in the serum, and this complex will then be excreted in the urine. Treatment with deferoxamine should be continued until symptoms resolve and urine is no longer discolored (pink/brown). [7] Children who are experiencing recurrent vomiting 2-6 weeks after ingestion should be evaluated for gastric outlet obstruction.[8]

Deferoxamine (Desferal) is an iron-chelating agent that is indicated for use in both acute iron intoxication and chronic iron overload.[9] This agent works by binding iron and forming a complex, which prevents the iron from participating in chemical reactions.[9] This agent does not affect iron that is bound by transferrin, cytochromes, or hemoglobin.[9] In addition, this medication does not affect the excretion of other electrolytes or trace metals.[9] Metabolism of deferoxamine is not yet understood; however, the formed complex is excreted primarily through the kidneys, which gives urine a characteristic red color.[9] Due to its renal excretion, deferoxamine is contraindicated in patients with renal impairment or anuria.[9] In patients who receive deferoxamine in high doses, for long periods of time, or if this agent is

administered in patients with low ferritin levels, reversal ocular and/or auditory disturbances may be observed.[9] These may include: blurry vision, cataracts, decreased visual acuity, visual defects, scotoma, corneal opacities, retinal pigmentary abnormalities, tinnitus, and hearing loss.[9] Other adverse events that have been observed include increases in serum creatinine, acute renal failure, and renal tubular disorders.[9] In patients with low ferritin levels, high doses of deferoxamine may cause growth retardation, which may increase after a dose reduction.[9] Administration of high intravenous doses of deferoxamine may also cause respiratory distress syndrome. This agent should be administered intramuscularly (IM) or by slow intravenous (IV) or subcutaneous infusion to prevent flushing of the skin, urticaria, hypotension, and shock.[9] Intramuscular administration is preferred for all patients who are not in shock.[9] Safety and effectiveness of this product have not been established in patients less than three years old.[9] The dose of deferoxamine in the situation of acute iron intoxication is 1000mg IM followed by 500mg every 4 hours.[9] 500mg doses may be repeated every 4-12 hours as needed based on clinical response, with a maximum dose of 6000mg in 24 hours.[9] This medication should only be administered via an intravenous route when the patient is experiencing cardiac collapse. If the patient's condition improves then intramuscular administration should take the place of intravenous infusion.[9] Deferoxamine 1000mg (IV) should be administered at a rate not greater than 15mg/kg/hour followed by two doses of 500mg over 4 hours if needed.[9] Subsequent doses of 500mg may be given over 4-12 hours if required, with a total daily allowance of 6000mg within 24 hours.[9] There is currently no antidote for deferoxamine, but this agent is readily dialyzable.[9]

Adult patients with children at home should be made aware that this medication should be kept in a safe location, out of reach of the children. The safety cap should remain on any bottle of iron-containing products to impede children from opening and accessing its contents. Patients should be warned that if a child were to take this medication serious adverse events could occur, including death. If this is to happen, patients should give their child milk to drink immediately, which will decrease the acidity of the stomach and slow iron absorption. [10] It is suggested to gather the following information if possible; patient's age, weight, current condition, the name of the ingested product, the time the product was ingested, and the amount that was ingested.[11] Parents should seek medical attention immediately if the amount ingested is unknown or if the time from ingestion is unknown. Parents may be directed to triage.webpoisoncontrol.org and/or may be directed to call the poison control at 1-800-222-1222 or 911.[12]

Iron overdose in children is a prevalent issue throughout the nation, with many of these cases being preventable. Increasing knowledge in the community as to the serious implications after ingestion of iron containing products may aid in decreasing overdose cases. Major damage in an overdose situation can be seen mainly in the GI tract, liver, and heart. There are four phases that occur after ingestion of iron

that leads to adverse effects of toxicity. The final phase may take place up to 8 weeks after ingestion has occurred. It is also important to note, the second phase is accompanied by no symptoms, which may be mistaken for a resolution of toxicity when an unknown amount of iron was ingested. Careful monitoring of the child should occur to ensure the child's safety until it is known that serum iron is below a toxic level. Treatment options may include: whole bowel irrigation, gastric lavage, endoscopic removal, or chelation with deferoxamine. Medical attention should be sought immediately after it becomes known that an overdose has occurred. Parents and guardians of children should be made aware to contact poison control, 911, or bring their child to the nearest hospital.

References

1. Boyle JS. Pediatric Iron Toxicity. Medscape. 2016. Available from: http://emedicine.medscape.com/article/1011689-overview
2. Iron Toxicity. Medscape. 2016. Available from: http://emedicine.medscape.com/article/815213-overview
3. Shannon M. Ingestion of toxic substances by children. *NEJM*. 2000; 342(3): 186-91.
4. Layland FC, Rajniti P, Shivani S, et al. Iron Poisoning. *Poisoning in Children*. 2006; 43-7.
5. Baranwal AK, Singhi SC. Acute iron poisoning: Management guidelines. *Indian Pediatr*. 2003; 40:534–40.
6. Fine J. Iron Posioning. *Curr Probl Pediatr*. 2000; 71-90.
7. Riordan M, Rylance G, Berry K. Poisoning in children 3: Common medicines. *Archives of Disease in Childhood*. 2002; 87(5):400-2.
8. Andeson AC. Iron Poisoning in Children. *Current Opinion in Pediatrics*. 1994;6(3):289-94.
9. Sanofi-Aventis U.S. LLC. Desferol (deferoxamine). 2012 [rev. 2012 April; cited 2017]. In: DailyMed [Internet]. [2005]. [about 20 pages]. Bethesda (MD): National Library of Medicine (US). Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d91e16df-8daa-4cd2-86a2-273eaa2446e0
10. AAP. Accidental Iron Poisoning in Children, Report of Committee on Toxicology. *Pediatrics*. 1959; 24(3): 399.
11. Heller J, Zieve D, Ogilvie I. Iron Overdose. MedlinePlus- US National Library of Medicine. 2015.
12. Mekonnen S. Iron Poisoning. 2017. Poison Control. Available from: http://www.poison.org/articles/2014-jun/iron-poisonin