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Review
Derleme

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Iron poisoning

Demir zehirlenmesi

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Abstract

Iron, represented by Fe on the periodic table, is the fourth most common element found on Earth. Although it has important tasks in the human body such as oxygen transfer, DNA synthesis, and electron exchange, it may also become toxic and harmful in excess. The toxicity of iron poisoning starts to appear with an intake of 20 mg/kg of elementary iron ions, along with GIS symptoms. In iron poisoning, patients usually present with various clinical findings and symptoms such as nausea, vomiting, palpitation, metabolic acidosis, deteriorated respiration, or mental disorders varying up to coma. Intervention in all patients begins with ABC evaluation, obtaining vascular access, monitoring, and (if necessary) providing oxygen support. Endotracheal intubation can be considered to ensure airway security and avoid aspiration, especially for lethargic patients. After abdominal and intestinal lavage, IV support treatment can begin, considering the liquid-electrolyte deficiency of these patients. In patients with a poor general condition and toxic appearance, hemogram, serum iron levels, kidney function tests, liver function tests, serum electrolytes, coagulation panel, arterial or venous blood gas, lactate, and in women of childbearing age, β-Hcg tests should be obtained. Abdominal radiography can be planned in the early stage. In patients thought to have serious iron poisoning, chelation treatment with deferoxamine is administered without delay.
Keywords: Iron, Poisoning, Toxic

Öz

Demir, Dünya'da en yaygın bulunan dördüncü elementtir. Periyodik tablodaki sembolü Fe'dir. Demirin insan vücudunda oksijen transferi, DNA sentezi ve elektron değişimi gibi önemli görevleri olmasına rağmen, aşırı toksik ve zararlı etkileri vardır. Demir zehirlenmesinin toksisitesi 20 mg/kg elementer demir iyonu alımı ile ortaya çıkmaya başlar. Demir zehirlenmesinde hastalar, bulantı, kusma, çarpıntı, metabolik asidoz, bozulmuş solunum veya komaya kadar değişen bilinç bozuklukları gibi çeşitli klinik bulgular ve semptomlarla karşı karşıya kalabilirler. Tüm hastalarda müdahale, ABC değerlendirmesiyle başlar. Hastanın damaryolu açılır, monitörize edilir ve (gerekirse) oksijen desteği sağlanır. Endotrakeal entübasyon, özellikle bilinç bozukluğu olan hastalar için, hava yolu güvenliğini sağlamak ve aspirasyondan korumak için düşünülebilir. Barsak lavajı nedeniyle oluşabilecek sıvı-elektrolit eksikliği göz önünde bulundurularak IV destek tedavisi başlanabilir. Genel durumu kötü ve toksik görünümü olan hastalardan hemogram, serum demir seviyeleri, böbrek fonksiyon testleri, karaciğer fonksiyon testleri, serum elektrolitleri, pıhtılaşma panelleri, arteriyel veya venöz kan gazı, laktat ve çocuk doğurma çağındaki kadınlar için BetaHcg testi istenebilir. Ayakta direk batın grafisinde erken aşamada planlanabilir. Ciddi demir zehirlenmesi olduğu düşünülen hastalarda demir seviyesi nedeniyle deferoksamin ile şelasyon tedavisi gecikmeden geçilmelidir.
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Introduction

Iron, represented by Fe on the periodic table, is the fourth most common element found on Earth. Although it has important tasks in the human body such as oxygen transfer, DNA synthesis, and electron exchange, it may also become toxic and harmful in excess [1]. Iron changes from the ferric form to the ferrous form with oxidation, joins the hemoglobin structure, and plays a role in the mitochondria and cytochrome. While anemia may develop in cases of iron deficiency, hemochromatosis may be seen in excess iron accumulation. The human organism keeps iron balance under tight control because of all these important tasks.

While iron can be consumed from meat and meat products as Heme, it can also be consumed as non-Heme iron from plants. Only a small portion of the consumed iron is expelled from the body through feces, urine, and the skin. A vast majority is stored as ferritin or hemosiderin in myoglobin in the liver and bone marrow. Iron follows various routes based on its form after intake. If the consumed iron is Heme-based Ferrous iron (Fe II), it is absorbed from the enterocytes in the small intestines with Heme carrier protein 1. It uses the same route as non-Heme iron when in plasma. Non-Heme iron, a.k.a. Ferric iron (Fe III), must be converted to Fe II first to be absorbed by the enterocytes. Ascorbic acid and stomach acid are necessary in the process. Thanks to the reductase enzyme that performs this transformation, DCytb (duodenal cytochrome b), it is absorbed into the enterocyte as Fe II through the Divalent Metal Transporter 1 (DMT 1). Before transfer to the plasma from the enterocyte, it transforms into Fe III once again. Fe III is removed from the cell with ferroprotein, a substance found in reticuloendothelial macrophages and hepatocytes, especially in the placenta and intestine. Hepcidin, a hormone which is synthesized in the liver, reduces iron secretion into the plasma by affecting ferroprotein. It plays a crucial role in the iron balancing of organisms. Based on these hormonal control and transportation mechanisms, it can be stated that iron, consumed in either Heme or non-Heme form, is managed by binding. Despite these mechanisms of control, the saturation of transferrin, normally at 30% of that of iron, further increases saturation and can accumulate in organs like the liver and heart and create toxic effects by moving freely in the plasma. This tight control mechanism over the absorption, storage, and transportation of iron is particularly important because the human organism itself cannot produce it. A substantial portion of the iron taken orally is absorbed as needed through the duodenum. Iron absorption, which occurs in about 10-35% of enterocytes, can reach 95% in case of iron deficiency. However, controlled absorption from enterocytes in instances of excessive iron intake increase passive iron absorption.

Supportive iron preparations are used as medication in deficiency treatment or multivitamins. Because iron preparations or iron-consolidated multivitamins are taken at extreme doses, a total of 5,910 cases were reported in the United States in 2016, and it was determined that of these, 2,204 were under the age of 5 years, 119 were between the ages of 6 and 12 years, and 475 were between the ages of 13 and 19 years. While five of all cases had major complications, only one case ended in mortality [2]. To the contrary, no organ failure or death was encountered in a cohort study conducted on iron poisoning cases admitted to a hospital in the United Kingdom between 2008 and 2017 [3]. The prevalence of serious toxicity tied to the excessive use of iron for pediatric patients is less than that of adult poisoning with iron preparations. While mortality did not occur in any of the 195,780 patients in the United States within the pediatric age group and among those who incorrectly and excessively used iron preparations between 1983 and 1998, 60 of the 147,079 adult cases of poisoning with iron preparations during the same period were mortal [4]. Cases of iron poisoning are now less frequent, yet still preserve their importance.

Medication doses and forms of preparates were arranged to prevent cases of iron poisoning, which decreased its prevalence of and doctors' related experience. For this reason, there are challenges in early diagnosis and effective treatment. Emergency care physicians must not ignore iron poisoning in cases admitted with clinical symptoms such as metabolic acidosis, mental state degradation, hypotension, and shock.

The iron preparations can be classified in two groups: Ionic and nonionic. The ionic forms of iron are ferrous chloride, ferrous fumarate, ferrous gluconate, ferrous lactate, and ferrous sulfate [5]. The nonionic forms of iron are carbonyl iron and iron polysaccharide. These nonionic forms of iron contain more elementary iron, and their GIS absorption is more limited. Parenteral iron, used in patients with kidney failure and chronic anemia, can have side effects such as anaphylaxis and toxicity.

The toxicity of iron poisoning starts to appear with an intake of 20 mg/kg of elementary iron, and GIS symptoms can appear simultaneously [6]. Iron most accumulates in the stomach, liver, brain, heat, lungs, small intestine, and kidneys. Damage, edema, congestion, and necrosis can may develop in the GIS mucosa and hemorrhaging and lung edema may occur. A study conducted on mice observed that in cases of iron poisoning, myocardial contractility deteriorated and the sensitivity of myosin ATPase and myofibril to calcium reduced [7].

Clinical properties

In iron poisoning, patients may present with various clinical findings and symptoms, such as nausea, vomiting, palpitation, metabolic acidosis, deteriorated respiration, or mental disorders varying up to coma [8]. The clinical status of the patient can be examined in five phases: The gastrointestinal phase that develops between 30 minutes and 6 hours after intake, the latent phase that appears after 6-24 hours, the metabolic acidosis and shock phase that can be seen after 6-72 hours, the hepatotoxic-haptic necrosis phase that can occur after 12-96 hours, and, finally, the intestinal obstruction phase that can develop after 2-8 weeks [5]. In the first phase of iron intoxication, findings of local irritation such as nausea, vomiting, diarrhea, and abdominal pain occur. Nausea is one of the most important findings of iron intoxication. Patients generally appear toxic due to vomiting and diarrhea. Additionally, edema, transmural inflammation, ulcer, hemorrhaging and, in severe cases, infarction and necrosis can appear in the intestinal system due to iron preparations. If no GIS symptoms are observed in the patient six hours after iron intake, the possibility of serious iron poisoning reduces. GIS symptoms regress in the second phase of

iron poisoning, and latent phase, in which systemic effects do not yet emerge, begins. The toxic effect can continue at the cellular level and, as a result, may cause tachycardia, lethargy, and metabolic acidosis in the patient. Patients whose vital findings and condition are stable after the GIS symptoms regress generally have a good prognosis. The shock phase emerges within a few hours after the intake of high doses of iron and can also occur within 12-24 hours in moderate intake. Tissue performance deteriorates, metabolic acidosis occurs due to hypovolemia caused by fluid loss because of vasodilation, decrease in cardiac output, diarrhea, and vomiting. Lethargy, coma, hyperventilation, or seizure can develop due to systemic toxicity. The fourth phase of poisoning begins two or three days later and is characterized by hepatic failure. Hepatotoxicity and, progressively, liver failure may be observed as a result of the oxidative damage is caused by accumulation of excessive iron in the liver. The fifth phase of iron poisoning is characterized by ileus, which is rarely seen and occurs after 2-8 weeks. Ileus may be caused by stenosis during the repair process of the gastrointestinal system and forms due to scar tissue. However, cases of intestinal obstruction have been reported within a week after iron poisoning with iron tablets [9].

Diagnostic tests

Radiography

It could assist in showing the iron preparations because tablets contain high amounts of iron elements. However, the failure to see preparations in the direct radiography does not eliminate iron poisoning or excessive amounts of iron intake.

Laboratory

Different tests can be requested based on the clinical status of the patient or the consumed amount of iron in iron poisoning. In patients with poor prognoses, it is recommended to obtain hemogram and blood gas and monitor lactate levels. To determine fluid-electrolyte imbalances due to vomiting and diarrhea, plasma electrolyte levels are preferably analyzed. Beta-Hcg is obtained from women of childbearing age. Serum iron levels and liver function tests are useful with regards to hepatotoxicity [5]. The level of blood iron concentration reaches a peak level approximately 2-6 hours after the consumption of iron preparations. Previous studies have shown that, when the blood-iron concentration level is between 300 µg/dL and 500 µg/dL, GIS symptoms or a moderate systemic toxic effect develop. Between 500 and 1000 µg/dL, systemic symptoms and shock status occurs, and levels higher than 1000 µg/dL are related to morbidity and mortality. Although serum iron level has much importance in terms of intoxication, a lower serum iron level does not exclude a serious case of intoxication [10]. Elementary iron has 50% mortality with an intake at doses of 200-250 mg/kg, and mortality can occur at doses of 130 mg/kg in the pediatric age group [11].

The total iron binding capacity is no longer used in the diagnosis of iron poisoning.

Initial treatment

Intervention in all patients begins with ABC evaluation, obtaining vascular access, monitoring, and (if necessary) providing oxygen support. Endotracheal intubation can be considered to ensure airway security and prevent aspiration, especially for lethargic patients. With gastric and intestinal lavage, IV support treatment can begin, considering the liquid-electrolyte deficiency of these patients. In patients with a poor general condition and toxic appearance, hemogram, serum iron levels, kidney function tests, liver function tests, serum electrolytes, coagulation panels, arterial or venous blood gas, lactate, and for women of childbearing age, β-Hcg test can be requested. Abdominal radiography can be planned in the early stage. Patients in a generally good condition and who have vomited only once or twice are monitored for vital signs and serum iron levels. After the patient stabilizes, attempts can be made to reduce GIS absorption of excess iron by lavage of the stomach or the entire intestine. Orogastric stomach lavage must be performed in admitted patients in the first 1-2 hours after iron intake [12]. However, lavage may prove difficult due to the hard materials which cover iron tablets. Nonetheless, in cases of iron intake at fatal levels, intestinal irrigation is recommended [13].

Inducing vomiting with ipecac syrup should be discussed in patients with iron poisoning. While some publications claim that patients made to vomit with ipecac syrup can partially remove the iron preparations and that it has no meaningful effect on serum iron levels, there are some who recommend its use during the first 60 minutes in patients admitted to emergency department and who have a high intake history of iron preparations [12].

Endoscopic and surgical methods could be considered if there are iron preparations that adhere to the abdominal mucosa, remain in the gastrointestinal system, or if it cannot be removed through orogastric lavage and full intestinal irrigation.

Deferoxamine treatment

Deferoxamine has a high affinity to iron and is acquired through cultures of bacteria called Streptomyces Pilosus. It is a white-yellow colored substance in a $C_{25}H_{48}N_6O_8$, CH_4O_3S structure, with an atomic mass of 656.8 daltons. It dissolves in water and alcohol, and is used as a chelator in iron poisoning [14]. It forms the ferrioxamine complex by combining with Fe^{+3}. In this regard, it effectively removes both intra- and extracellular iron by binding. But the penetration into the cell due to its hydrophilic structure is low [15]. As much as 100 mg of deferoxamine binds approximately 8.5 mg of Ferric iron. A prospective study conducted with non-transfusion dependent thalassemia patients concluded that the iron load in the liver was reduced with a deferoxamine chelation [16].

In patients thought to have serious iron poisoning, chelation treatment with deferoxamine is administered without delay. If the serum iron level is greater than 350 mcg/dL in patients with toxicity findings but without clinically very serious symptoms or greater than 500 mcg/dL In patients without any symptoms or findings, initiation of chelation treatment is recommended. Intravenous dose of deferoxamine should be titrated to 15 mg/kg/dour. In very serious iron poisoning, it can reach up to a dose of 35 mg/kg/hour in the first 24 hours. Only when the toxic appearance disappears, metabolic acidosis of the patient is corrected, or urine discoloration ends, should the deferoxamine infusion be stopped [10].

In case of serious iron poisoning during pregnancy, deferoxamine should be used without considering the status of the fetus. The treatment of these patients is the same as other

patients. Previous animal studies have not shown that deferoxamine or excessive iron intake has a negative effect on the fetus.

In the pediatric age group, exchange transfusions can be useful in situations where deferoxamine is insufficient [17].

Hemodialysis

Hemodialysis only affects the elimination of freely circulating iron, and its benefit is limited because it has no effect in removing excessive intracellular iron from the body. A decrease in iron levels and clinical improvements were reported when hemodialysis was implemented in addition to deferoxamine for patients with life-threatening findings after receiving excessive doses of iron [18]. Hemodialysis can be considered especially in patients with levels of serum iron higher than 1000 mcg/dL [11].

Discharge

Asymptomatic patients, those who have received less than 40 mg/kg of iron element, whose intake amount is unclear but have a blood-iron level of less than 500 mcg/dL and in those which iron preparations are not observed in the Standing Direct Abdominal Radiography are kept under six hours of observation. These patients can be discharged if their asymptomatic state continues. Mildly symptomatic patients, those who received more than 40 mg/kg of elementary iron, those with an unclear amount of intake but have a blood-iron concentration of less than 500 mcg/dL and in whom iron preparations are not observed in the Standing Direct Abdominal Radiography are monitored for 6-12 hours. Unstable patients, patients with anion gaps, metabolic acidosis, or lethargy, or those who are in shock are should be monitored in the intensive care unit [5].

Conclusion

Iron preparates are common and widely used. Serious negative consequences can occur, either intentionally or because of misuse. Physicians should pay attention to iron poisoning, know the emergency approach to such patients, and keep iron poisoning in mind for differential diagnosis. Early intervention plays a significant role in diagnosing and treating the disease.

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