Iron deficiency anaemia

By Katie Hayes

Case details

Jennifer is a 36-year-old regular customer of the pharmacy, who lives with her husband and two children. She has a past medical history which includes depression, anxiety, gastro-oesophageal reflux disease, endometriosis, asthma, migraine and a shoulder injury. Jennifer had a hysterectomy about six months ago and has undergone several surgical procedures since, for infection at the site of hysterectomy. She is also scheduled to have surgery on her shoulder to repair a suspected torn cartilage.

Learning objectives

After reading this article you should be able to:

- Identify signs and symptoms of iron deficiency anaemia
- Describe the pharmacological management options in iron deficiency anaemia
- Identify possible adverse effects of iron administration.

Competency standards (2010) addressed:
7.1.1, 7.1.2, 7.1.3, 7.1.4

Accreditation number: CAP110606g

Jennifer’s current medications are:

- esomeprazole 40 mg, one tablet daily
- diclofenac 50 mg, one tablet daily
- paracetamol 500 mg/codeine 30 mg, two tablets taken three times daily
- oxycodone 5 mg, one tablet twice daily when required (infrequent use)
- salbutamol 100 mcg MDI, one puff to be taken occasionally when required
- zolpidem CR 12.5 mg, one tablet at night when required (uses about twice a week)
- Metamucil capsules, one capsule daily
- senna 7.5 mg, two tablets daily
- multivitamin tablet, one tablet on alternate days

Jennifer is currently suffering from constipation due to her medications, her diet, lack of exercise, and her recent surgical procedures. She currently has iron deficiency anaemia, as indicated by her laboratory results (see Table 1). She is not taking iron tablets at present, as they may worsen her narcotic-induced constipation. Jennifer complains of feeling tired and lethargic and lacks appetite; she is noticeably pale and looks visibly thinner than usual. She has noticed hair loss recently; and although she describes being in a low in mood, she states that she doesn’t want to take medication for this at present.

Iron deficiency anaemia

Iron deficiency is a common cause of anaemia in Australia.1 It is caused by inadequate iron intake, inadequate iron absorption and/or excessive iron loss.2 Iron is required for the production of haemoglobin and myoglobin, and the clinical consequences of deficiency tend to be a result of the reduced levels of these two proteins.

Diagnosis

Early in deficiency, patients generally have mild signs and symptoms such as fatigue or lethargy.3 As deficiency
**Table 1. Blood test results for Jennifer**

<table>
<thead>
<tr>
<th>Pathology test</th>
<th>Result</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>haemoglobin (Hb)</td>
<td>105 g/L</td>
<td>adult female: 115–165 g/L</td>
</tr>
<tr>
<td>haematocrit (Hct)</td>
<td>0.31</td>
<td>adult female: 0.37–0.47</td>
</tr>
<tr>
<td>mean cell volume (MCV)</td>
<td>79 fL</td>
<td>80–100 fL</td>
</tr>
<tr>
<td>platelet count</td>
<td>147 x 10^9/L</td>
<td>150–400 x 10^9/L</td>
</tr>
<tr>
<td>red cell count (Rcc)</td>
<td>3.6 x 10^12/L</td>
<td>adult female: 3.8–5.8 x 10^12/L</td>
</tr>
<tr>
<td>white cell count (Wcc)</td>
<td>7.3 x 10^9/L</td>
<td>4–11 x 10^9/L</td>
</tr>
<tr>
<td>iron</td>
<td>9 micromol/L</td>
<td>10–30 micromol/L</td>
</tr>
<tr>
<td>transferrin</td>
<td>3.1 g/L</td>
<td>1.7–3.0 g/L</td>
</tr>
<tr>
<td>ferritin</td>
<td>14 microgram/L</td>
<td>15–200 microgram/L</td>
</tr>
</tbody>
</table>

progresses, the symptoms usually become more severe and serious and may include chest pain and shortness of breath. The general signs and symptoms of iron deficiency anaemia are listed in Table 2.

Blood test results that may indicate iron deficiency anaemia include: low haemoglobin, low mean corpuscular volume, low ferritin, high transferrin, high total iron binding capacity (TIBC), low transferrin saturation. Ferritin is a globulin protein that binds iron in the plasma and transports it to the bone marrow in readiness for red blood cell production. Ferritin is the major iron-storage protein and is indicative of total body iron stores – this tends to be reduced in iron deficiency anaemia. Ferritin levels tend to reduce before other laboratory indicators of iron deficiency and is the most reliable indicator of iron deficiency anaemia. TIBC indicates the quantity of proteins which are available for binding mobile iron and are these usually elevated in iron deficiency anaemia.

**Table 2. Signs and symptoms of iron deficiency anaemia**

<table>
<thead>
<tr>
<th>Appearance</th>
<th>Tired, listless, lifeless</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Pale, inelastic, dry</td>
</tr>
<tr>
<td>Hair</td>
<td>Thinning</td>
</tr>
<tr>
<td>Mouth/ gastrointestinal tract</td>
<td>Glossitis, oesophageal webbing, angular stomatitis, gastric atrophy, angular cheilitis, tongue erythema</td>
</tr>
<tr>
<td>Eyes</td>
<td>White or pale blue sclerae</td>
</tr>
<tr>
<td>Nails</td>
<td>Brittle, concave (koilonychia), flattened</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Tachycardia, slight cardiomegaly</td>
</tr>
<tr>
<td>Oral intake</td>
<td>Pica: unusual craving for substances with no nutritional value including (e.g. clay, paper, ice, paint, starch)</td>
</tr>
<tr>
<td>Spleen</td>
<td>Splenomegaly in severe, untreated disease</td>
</tr>
</tbody>
</table>

**Treatment**

It is important to establish the cause of the iron deficiency anaemia because treatment may not be successful or the anaemia may return if the cause is not corrected. Common causes are inadequate dietary iron intake, problems with absorption or more serious causes such as gastrointestinal bleeding. The treatment of iron deficiency anaemia depends largely on severity at time of diagnosis.

**Oral iron supplementation**

A mild iron deficiency anaemia, which is identified through laboratory results because few symptoms are evident, can be treated with oral iron supplementation. The recommended dose for iron supplementation is 100–200 mg of elemental iron daily. Correct administration of oral iron replacement is important to increase its effectiveness and where possible should be taken on an empty stomach to maximise absorption. However, many individuals experience side-effects such as abdominal pain, nausea, vomiting, constipation and/or diarrhoea – in this situation iron supplements can be taken with food to enhance compliance, albeit with reduced iron absorption expected. Oral iron supplements may bind with some medications and reduce both their activity (e.g. tetracyclines and quinolones) and the amount of iron absorbed. Some medications may decrease the activity of iron e.g. calcium supplements and antacids. Other medications, for example, thyroid hormones, bisphosphonates, methyldopa and levodopa have their activity reduced by the concurrent administration of oral iron supplements. Iron supplements should be spaced several hours away from all these medications so that the efficacy of both is retained.

**Injectable iron supplementation**

Patients who cannot tolerate oral iron therapy or who have more severe iron deficiency, can be administered parenteral iron. In Australia, there are two preparations of parenteral iron available: iron polymaltose complex (also known as iron dextrin) and iron sucrose.

Whenever parenteral iron is required, intravenous (IV) administration is recommended over intramuscular (IM) administration due to poor iron absorption, injection site pain and skin discolouration from IM administration. In the general practice clinic however, IM iron administration is practical and the use of correct injection technique will minimise these adverse effects. Adverse reactions that are associated with parenteral iron administration include nausea, vomiting, headache, hypotension, hypertension, tachycardia, bradycardia, fever, chest pain, rash and angioedema.

Reported adverse reactions to different iron complexes used internationally include: iron dextran 50%, iron sucrose 36% and ferric gluconate 35%. Intravenous iron sucrose has a lower risk of adverse effects than IV iron polymaltose. Iron dextran has been associated with anaphylaxis in 0.6–0.7% of patients, 0.002% in patients who are administered iron sucrose and 0.05% in patients administered with ferric gluconate with the frequency of serious or life-threatening reactions caused by ferric gluconate and iron sucrose considered rare.
The cause of the anaphylaxis with iron dextran is thought by some to be attributed to the dextran moiety as opposed to iron itself. There is some evidence however, that toxicity rather than anaphylaxis may cause adverse reactions due to a greater number of reactions occurring with an increase in the dose and infusion rate, but some of adverse effects indicate allergy-related mechanisms and include; bronchospasm, angioedema and urticarial and both mechanisms should be considered when assessing a patient experiencing adverse effects. There has been a significant reduction in the rate of adverse reactions, particularly serious reactions, since the administration of iron polymaltose largely replaced that of iron dextran. One audit examining 401 infusions in 386 patients found that there were no incidences of anaphylaxis or cardiorespiratory issues in patients administered total dose iron polymaltose infusions, and the side-effects that were experienced were mild and infrequent. A quality assurance project conducted in a primary care clinic in Sydney with 43 adult patients given a total or 89 IV iron polymaltose injections found that no serious reactions occurred. Similar findings have since been reported in other trials. While intravenous iron sucrose is associated with fewer cases of anaphylaxis than iron polymaltose, it is expensive and there are PBS-restrictions on its supply.

There are other iron preparations available internationally, for example, a new preparation iron carboxymaltose, can be given as 1,000 mg over 15 minutes and thus far, appears to have a low risk of serious adverse reactions. The fear of adverse effects that accompanies parenteral iron therapy is probably unnecessary due to the low rate of serious adverse effects provided appropriate supportive therapy is available should a rare anaphylactic reaction occur.

Calculating parenteral iron dosing

Total dose infusion, where the total amount of iron required for replacement is administered in one infusion, can only be used for patients receiving iron polymaltose. A maximum of 2,500 mg can be given as an IV infusion in 500 mL of 0.9% sodium chloride. Iron polymaltose may also be given intramuscularly at a dose of 100 mg every second day until the total dose is reached. Administration protocols vary and local guidelines should be followed.

As published in the manufacturer’s product information, the dose required of iron polymaltose complex needed to correct deficiency can be calculated using the Ganzoni formula:

\[ \text{Iron dose (mg)} = \text{bodyweight (kg)} \times [\text{target Hb} – \text{actual Hb (g/L)}] \times 0.24 + \text{iron depot} \]

The Gastrointestinal Therapeutic Guidelines contains a table which provides guidance on the recommended dosing of iron polymaltose, based on calculations using the Ganzoni formula.

The potential for intravenous iron administration to cause serious adverse effects can be minimised by the use of a test dose or commencing infusions slowly which is recommended in various hospital protocols.

For iron sucrose, a test dose of 20 mg is diluted to a maximum of 20 mL in 0.9% sodium chloride and administered over 15 minutes. The recommended dilution for treatment doses is 100 mg iron sucrose diluted to 100 mL with 0.9% sodium chloride and administered by IV infusion over 15 minutes with dilution occurring immediately before administration.

Iron infusions should not be mixed with other agents due to the potential for production of toxic compounds.

Other treatments

Where patients have severe iron deficiency anaemia, a blood transfusion should be considered and is recommended when the haemoglobin level is below 70 g/L. Erythropoietin (EPO) agonists stimulate erythropoiesis which leads to an increase in reticulocyte count and therefore increases the concentration of haemoglobin and haematocrit in the blood. They are indicated in some forms of anaemia, including anaemia of chronic renal failure, but their use for uncomplicated iron deficiency anaemia is not widespread due to expense and safety concerns.

Case discussion

It is likely that some of the signs and symptoms that Jennifer is experiencing (e.g. lethargy, pallor and hair-loss) are at least in part due to iron deficiency anaemia.

The dose of Metamucil that Jennifer is taking is less than adequate as a fibre supplement and is unlikely to treat her constipation at this stage; but may be useful as a prevention therapy in an adequate dose once constipation is resolved. Jennifer was considerably constipated, as indicated by her description of hard stools that are difficult to pass despite adequate water consumption. The senna she has been taking has not been effective, possibly due to the difficulty of passing the stool. It may be beneficial to try a laxative that increases fluid content of the stool such as a polyethylene glycol laxative.

Lifestyle changes would be beneficial to Jennifer including restarting of an exercise program and increasing the total consumption of food especially those foods rich in fibre (e.g. vegetables, fruits, rye and barley) and iron (e.g. red meat, chicken and spinach). Inadequate water consumption is not likely to be contributing to her constipation as she already consumes two to three litres of water daily.

Actions and recommendations

Due to Jennifer’s inability to tolerate oral iron supplements, and in preparation for her imminent surgical procedures, administration of IM iron supplementation should be considered; as this can be given in an appropriately equipped general practice. Correct injection technique is vital to reduce the risk of persistent skin discolouration and pain. Detailed instructions are provided in manufacturer’s information and includes advice on injection site, length of needle, vertical needle insertion, application of pressure after injection and encouraging movement of the patient after injection.

For treatment of Jennifer’s constipation it was suggested that an osmotic laxative such as Movicol be used to increase the fluid content within the stool. She was advised to use the powdered form of Metamucil and to take the recommended amount to ensure appropriate dosing, as well as maintaining her water intake.
Jennifer agreed to start walking every day in an attempt to regain her fitness, promote sleep and help constipation. She also said that she would increase her food intake, particularly of iron- and fibre-rich foods as she understood that this would assist in recovering from anaemia and constipation and would make the use of the multivitamin unnecessary.

Outcomes

At this stage the doctor wished to continue monitoring Jennifer’s haemoglobin and haematocrit; rather than actively manage her iron deficiency anaemia with IM administration of iron (either in the surgery or on referral to hospital due to concern over the potential for adverse reactions). The doctor was informed about the actual rate of reaction, but wished to have this addressed in hospital when Jennifer was next admitted for surgery. It was also mentioned in the report that serum iron, ferritin and TIBC should also be monitored; as these are more indicative of iron deficiency anaemia, whereas low levels of haemoglobin and haematocrit can occur with other forms of anaemia.

The doctor acknowledged the need to treat Jennifer’s constipation especially considering the plan for more surgical treatment further increasing the risk of constipation. He suggested that she return to her community pharmacy to purchase Movicol and adjust her diet as had been recommended.

Jennifer mentioned on one of her visits to the pharmacy that her appetite had increased and she was feeling much better.

Summary

Parenteral iron administration is currently avoided due to the fear of serious adverse effects from the treatment. In reality, the incidence of serious adverse effects is minimal and in an appropriately equipped setting can be undertaken safely and should be considered as an alternative in patients who do not get the required results from oral iron administration or who cannot tolerate oral iron therapy.

References

19. Iron polymaltose infusions discussion paper: Rapid response to iron polymaltose infusion e-mail discussion. NSW Therapeutic Advisory Group; 2008:1.
27. eMIMS: Prescribing Information: Movicol Monograph. St Leonards, NSW: MediMedia Australia; 2010 [cited 2011 Apr].

Questions

1) Signs and symptoms of iron deficiency anaemia include:
   a) diarrhoea, stomach cramps and nausea.
   b) fatigue, lethargy and hair loss.
   c) shortness of breath, elevated blood pressure and insomnia.
   d) fever, rash and angioedema.

2) What initial recommendation is MOST SUITABLE for a patient who suffers from nausea and stomach pains after taking oral iron supplementation?
   a) Advise the patient to stop taking iron therapy.
   b) Advise the patient to take the iron supplement with food.
   c) Refer the patient to the doctor as these symptoms are only caused by gastroenteritis.
   d) Advise the patient to take the iron for parenteral iron therapy.

3) Which of the following statements is TRUE?
   a) Iron carboxymaltose is a new iron preparation, but has a high rate of adverse effects.
   b) Iron sucrose can be given IM or IV.
   c) A test dose of IV iron, or introducing the infusion slowly, is recommended at the beginning of an IV infusion to minimise the potential for anaphylaxis.
   d) Iron polymaltose complex cannot be given as a total dose infusion.
   e) The rate of anaphylaxis with IV iron administration is:
      a) 0.7% with ferric gluconate.
      b) 0.002% with iron polymaltose complex.
      c) 0.7% with iron sucrose.
      d) 0.002% with iron sucrose.
   f) The most reliable indicator of iron deficiency anaemia is:
      a) ferritin.
      b) transferrin.
      c) haemoglobin.
      d) haematocrit.