Managing anaemia in renal failure

In May 2004 updated European Best Practice Guidelines for the management of renal anaemia were published. **John Sexton** and **Marc Vincent** review the management of this condition

Anaemia (a reduced blood haemoglobin [Hb] concentration) is a common problem in chronic kidney disease (CKD), leading to substantial morbidity and mortality if untreated. Over the past decade, effective management has become possible using safer intravenous iron preparations and genetically engineered erythropoiesis-stimulating agents (ESAs).

To ensure safe and effective management, treatment should follow established guidelines and the latest of these, the European Best Practice Guidelines (EBPG)[1] were published in May 2004. The Renal Association last published its standards for the UK (RAS)[2] in August 2002 and differences between the RAS and EBPG will be mentioned here.

The National Institute for Clinical Excellence (NICE) is not due to publish a clinical guideline on renal anaemia until the second half of 2006.

Aetiology

Anaemia was formerly a classic and serious complication of CKD, caused and aggravated by a variety of factors:

- Stress ulceration, seen in many other chronic conditions, can lead to subclinical gastrointestinal blood loss
- Proton-pump inhibitors (commonly prescribed in CKD to treat stress ulceration) reduce iron absorption from the gastrointestinal tract
- Modified diets intended to reduce phosphate or protein can also affect levels of dietary iron (phosphate accumulates in renal failure and reducing excessive protein intake can slow progression of renal failure)
- Uraemia (accumulation of metabolic nitrogenous waste) often leads to anorexia and nausea which may further reduce oral iron intake and absorption
- Phosphate binders, which many renal patients are prescribed, such as calcium and aluminium salts, also reduce iron absorption from the gut
- Haemodialysis, which leads to patients losing some functioning erythrocytes in each session, even if there is no clotting during dialysis or a haemorrhage induced by the anticoagulants administered to facilitate haemodialysis
- Overzealous blood sampling for analysis, especially among inpatient populations, can remove substantial amounts of blood over time
- Infections, inflammation, uraemia, hyperaluminiumaemia, hyperparathyroidism and other disturbances in blood chemistry that affect the ability of the bone marrow to make erythrocytes can lead to anaemia even in iron-replete patients

Even if all the above factors are well controlled, anaemia is still common in patients with severe CKD. The peritubular cells of the failing kidney are unable to secrete sufficient erythropoietin, the hormone that stimulates erythropoiesis (manufacture of erythrocytes). It is important that anaemia in patients with CKD is investigated thoroughly because it might also indicate a potentially serious underlying non-renal morbidity. A diagnosis of anaemia due to deficient erythropoietin should only be made in patients with CKD in whom no other cause of anaemia can be identified.

Presentation

Anaemia is considered to be present when blood Hb concentration is reduced to a level below that necessary for adequate tissue oxygenation.

The EBPG say that anaemia should be investigated in patients with CKD when Hb levels fall below:

- 11.5g/dl in adult females
- 13.5g/dl in adult males
- 12g/dl in adult males aged over 70 years

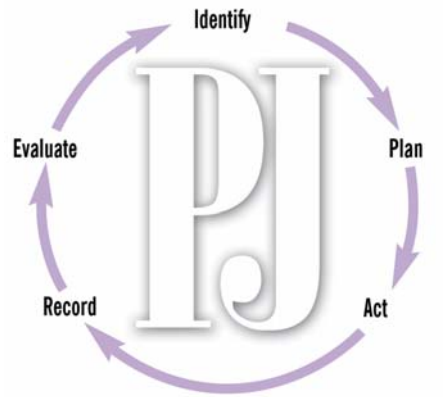
The RAS are more conservative. Reference ranges for Hb in people without CKD are typically between 12 and 15g/dl in adult females and 13 and 17g/dl in adult males, depending on the laboratory quoted. Anaemia progresses with the decline in renal function.

Hb typically falls below 11g/dl as the glomerular filtration rate (GFR) drops below 30ml/min. Patients with diabetes tend to develop anaemia earlier and to a greater degree than patients without diabetes.

The signs and symptoms of anaemia vary with severity and the period over which the reduction in Hb develops. Anaemia of CKD may present with:

- Mild breathlessness on exertion
- Lethargy
- Tiredness

John Sexton, MSc, MRPharmS, is principal pharmacist lecturer-practitioner at the Royal Liverpool and Broadgreen University Hospitals NHS Trust and Liverpool John Moores University
Marc Vincent, BPharm, MRPharmS, is senior renal services pharmacist at the Royal Liverpool and Broadgreen University Hospitals NHS Trust



Identify knowledge gaps

1. Why do patients with chronic renal failure develop anaemia and what are the consequences if this remains uncorrected?
2. What products are licensed for the management of renal anaemia and how are they used?
3. What monitoring is required to ensure the desired outcomes of therapy for renal anaemia are achieved?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: www.rpsgb.org/education). This article relates to "common disease states and their drug therapies" (see appendix 4 of "Plan and record").

However, due to its insidious onset, anaemia associated with CKD is often asymptomatic and only picked up upon routine blood analysis. Alternatively, presentation might include precipitation of angina or pulmonary congestion.

If left untreated, anaemia is associated with many complications including increased cardiac output leading to cardiac enlargement and heart failure, cognitive impairment, altered menstrual cycles, erectile dysfunction and impaired immune response.

Target haemoglobin

Due to the high cost of therapy with ESAs, target Hb concentrations in the guidelines are based on the minimum proven to be of measurable benefit. The RAS recommend a target Hb of >10g/dl, which should be achieved within six months of seeing a nephrologist. The EBPG advise a higher target level of >11g/dl within four months of starting therapy with the agents and this standard is now followed by most renal units in

All patients requiring ESAs should receive them in the appropriate doses

the UK, at least for dialysis patients. Earlier concerns regarding hypertension and thrombosis at Hb levels >10g/dl have lessened.

The maximum desirable Hb level in a patient is still a contentious issue because of the paucity of the evidence base. However, the EBPG recommend limiting Hb levels to <14g/dl in haemodialysis patients due to post dialysis haemoconcentration and the potential risk of thrombosis, and <12g/dl in patients with severe cardiovascular disease or in diabetic patients with peripheral vascular disease.

Iron therapy

Patients with CKD are at increased risk of iron deficiency. In particular, patients receiving haemodialysis have iron requirements around three times greater than normal healthy subjects.

The rapid increase in erythropoiesis on initiation of ESAs rapidly depletes existing iron stores so it is sensible to ensure these are adequate before ESA therapy starts. In addition, if the anaemia is due to iron deficiency rather than the presumed erythropoietin deficiency, Hb will start to rise once iron stores are adequate — the most common cause of epoetin-resistance is iron deficiency.

Iron deficiency can be either "absolute" (due to depletion of iron stores) or "functional" (due to inadequate mobilisation of iron stores to support the acute demands of ESA therapy) but both can be treated with iron therapy. In fact, all patients treated with ESAs require maintenance iron supplements to sustain efficient erythropoiesis. Oral iron preparations can be sufficient in non-dialysing patients and those on peritoneal dialysis but periodic intravenous therapy might be required. Haemodialysis patients have increased requirements because of blood loss on dialysis and almost always need intravenous therapy with iron sucrose or iron dextran.

Oral iron is frequently associated with gastrointestinal intolerance including nausea, vomiting, abdominal pain and constipation, resulting in poor compliance. Intravenous therapy is more effective but has its own limitations. Iron sucrose is generally considered the safer preparation but both iron sucrose and iron dextran products raise concerns because of rare, but life-threatening, anaphylactic reactions. For both preparations, a test dose of 25mg is, therefore, given on initiation of therapy. The dosage regimen for iron therapy is individualised and based on a patients "iron studies" but haemodialysis patients often require regular doses of up to 100–200mg weekly. Iron studies include measuring serum iron concentration, total iron binding capacity (TIBC) and, in particular, percentage transferrin saturation (TSAT) and serum ferritin. For patients on ESAs to achieve and maintain target Hb values sufficient iron should be administered to maintain a TSAT of >20 per cent and serum ferritin of >100µg/L (see Panel 1).

ESA therapy

Treatment of anaemia with ESAs has led to increased quality of life and a reduced cardiovascular disease risk. Risk of cardiovascular disease normally increases with declining renal function and is the leading cause of mortality among patients on dialysis. Treatment means that the need for blood transfusions to correct anaemia is reduced, decreasing the risks of transmission of blood-borne viruses, iron overload and sensitisation of patients to future transplants. ESAs also have a positive impact on exercise capacity, sleep patterns, cognitive function, immune response and sexual function.

ESA therapy may not be necessary in all patients, particularly those on peritoneal dialysis and those not yet requiring dialysis, especially if they are well nourished and iron replete and (if dialysing) well dialysed. ESAs should be given to all patients with CKD whose Hb levels are consistently below 11g/dl and where other causes of anaemia have been excluded. There is no doubt of the benefits of ESA therapy in pre-dialysis patients and use is becoming common despite funding streams often being hard to identify in this population.

In practice, since most patients now start ESA therapy before dialysis they will initially receive it subcutaneously. After correcting iron deficiencies, the manufacturers advise ESA starting doses based on weight; epoetin beta subcutaneously 60units/kg/week, usually given in three divided doses, or darbepoetin 450ng/kg, once weekly. In practice, clinicians tend to opt for simpler starting doses for most patients, such as epoetin beta 2,000 to 3,000 units three times per week. The aim of therapy is to achieve a 1 to 2g/dl/month rise in the Hb level until the target level is achieved. More rapid correction is undesirable and can result in uncontrolled hypertension or thrombosis. Hb levels should be monitored regularly and doses increased or decreased in increments of 25 per cent to achieve targets.

The most common adverse effect is hypertension, particularly if Hb levels increase too rapidly. Blood pressure should be monitored closely in all patients with CKD, especially during initiation of ESAs. If hypertension does occur this should be managed aggressively, without compromising ESA therapy where possible.

Panel 1: Iron studies

Serum ferritin Serum ferritin is an iron storage protein, which provides an indirect measurement of stored iron. A low serum ferritin level is always indicative of iron deficiency. A high serum ferritin (>800µg/L) does not always indicate iron overload because levels are also raised if there is hepatocellular injury or inflammation. Ferritin levels can also be falsely high for up to one week after intravenous iron administration. Patients on haemodialysis often have raised serum ferritin levels but this is rarely due to iron overload and more likely to be due to low-grade inflammatory processes.

Transferrin Transferrin is a protein that transports iron from stores to the bone marrow. Transferrin saturation gives a measure of iron available to the bone marrow. This makes it a useful parameter for detecting functional iron deficiency. Functional iron deficiency can exist despite normal or raised ferritin values. Iron availability can be more accurately assessed by measuring the percentage of circulating hypochromic red blood cells (%HRC) but the availability of the special analysers to carry out this test is still low in the UK. The %HRC directly reflects the proportion of cells with a sub-optimal Hb concentration and a measurement of >10 per cent indicates definite functional iron deficiency.

Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Familiarise yourself with the doses, side effects and uses of the erythropoietic agents used in renal anaemia
2. Check cold-chain distribution arrangements and sharps disposal for any patients receiving epoetin or darbepoetin
3. Access the Medicines Management Framework for renal services (available at www.dh.gov.uk) and identify some general counselling points in renal patients.

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities.
Answer the following questions:
What have you learnt?
How has it added value to your practice? (Have you applied this learning or had any feedback?)
What will you do now and how will this be achieved?

Panel 2: Epoetin and darbepoetin — a brief history and comparison

Epoetin The correlation between altitude-induced hypoxia and increased red blood cell (RBC) counts was first observed in 1882, but the hormone responsible for RBC formation, erythropoietin, was only purified and analysed in 1977. By 1985 the gene responsible for the manufacture of erythropoietin had been identified and, in 1988, Amgen launched the first recombinant human erythropoietin (rHuEPO), epoetin-alfa in the US. This was licensed to Janssen-Cilag (now Ortho-Biotech) which brought it to the European market as Eprex. Subsequently the German company Boehringer-Mannheim, now part of Roche, marketed epoetin-beta (NeoRecormon).

Epoetin is an expensive therapy, and patients can require epoetin costing £3,000–£4,000 or more annually. Expenditure is rising as eligible patient numbers increase and the specified target haemoglobin levels are also raised.

Epoetin-alfa and beta were originally licensed for haemodialysis patients, whose anaemia is made worse by the inevitable blood losses involved in that procedure. Use has since extended into peritoneal dialysis populations and patients with chronic renal impairment not severe enough to warrant dialysis, the so-called "pre-dialysis population". Similarly, the range of presentations has extended into pre-filled syringes and, for NeoRecormon, multiple-dose vials and pens.

Both epoetins were originally administered by either the intravenous or subcutaneous routes but, in 2002, Eprex had its subcutaneous licence revoked following the increase in reported cases of pure red cell aplasia (PRCA). PRCA is much less frequently reported in patients treated with epoetin-beta, the newer alternative darbepoetin and the Amgen-made epoetin-alfa (still used in the US). The increased incidence has been attributed to a change in formulation of Eprex in 1998 in which albumin was removed. Eprex remains licensed for intravenous use, where the risk of PRCA is not considered higher than with other ESAs but, in practice, this restricts its use to haemodialysis patients with intravenous access only.

Both epoetin-alfa and beta have the same amino-acid sequence as natural erythropoietin, differing only in glycosylation. This does not seem to matter in practice, although the British National Formulary has always specified that the two products are not interchangeable.

Darbepoetin In 2001, Amgen launched a novel erythropoiesis stimulating protein (NESP), darbepoetin-alfa, which it marketed as Aranesp. Darbepoetin has a slightly different amino acid sequence from the natural hormone, allowing additional carbohydrate chains to be attached. This prolongs the terminal half-life to about three times that of epoetin.[3] After three years, the UK market is now currently equally divided between epoetin and darbepoetin. At a local level, the rise of regional hospital purchasing contracts, led by substantial discounts available for bulk purchases, has led to the predominance of one product or another in many areas.

Darbepoetin vs epoetin Although comparisons of darbepoetin with epoetin suggest that achievement of desired haemoglobin outcomes, adverse-events and costs are broadly similar, there may be some differences with epoetin-alfa and beta:

Administration Traditionally, epoetin was administered three times a week. Although NeoRecormon is now licensed for weekly use, once target haemoglobin has been achieved (and even every two weeks if patients have proved stable on weekly dosing), epoetin doses might need to be increased substantially to allow this. Darbepoetin has a longer half-life. It is licensed for weekly use from initiation (every two weeks in non-dialysing patients) so patients require fewer injections. Stable non-dialysing patients may receive darbepoetin as infrequently as once a month, as do dialysing patients in many centres, although the latter is outside the current product licence.

If epoetin is given intravenously to haemodialysis patients, a substantial increase in dose (and, therefore, cost) might be required to counteract a loss of efficiency. Epoetin-beta is, therefore, still given by the subcutaneous route to many patients who could receive it painlessly down their haemodialysis lines. With darbepoetin, this loss of effect is not seen and so intravenous administration on dialysis is facilitated without a cost increase.

Cost Amgen priced Aranesp to be the same cost as NeoRecormon and Eprex at the standard 1:200 weekly dose conversion based on molecular mass. Different studies have suggested that this ratio may not always apply in different patients groups.

Storage The summary of product characteristics for Aranesp allows it to be kept for seven days at room temperature (below 25C),as long as syringes are not returned to the fridge afterwards. The summary also lets patients warm their syringes (by standing for 30 minutes) to room temperature so that injections are less painful. NeoRecormon pre-filled syringes can be removed from the fridge for up to three days, but Eprex has no room temperature allowance. Given that instability of the ESA molecules is postulated as a cause of PRCA, these cold chains are important, as is not shaking the syringes.

In the near future epoetin may be available as a dry powder injection, and Roche is developing the continuous erythropoietin receptor agonist (CERA).[3] CERA is a molecule that might allow therapy to be administered monthly at most, and may reach the market within two or three years. However, most of the development of ESAs will be in expansion of their use. Although some products are also licensed for non-renal indications (eg, in oncology, haematology, and to facilitate the harvesting of autologous blood before surgery), most use remains in patients with chronic renal failure.

ESA resistance Resistance to ESAs should be considered if a patient fails to achieve target Hb level, despite receiving more than 20,000 units of epoetin beta or 100µg of darbepoetin per week. Any condition that predisposes patients to anaemia will inevitably create an inadequate response to ESA therapy, including deficiencies in iron, vitamin B_{12} and folate.

Other causes of ineffective therapy include inadequate dialysis, parathyroid overactivity, aluminium toxicity, chronic blood loss, multiple myeloma and other malignancies, therapy with immunosuppressive agents or angiotensin-converting enzyme inhibitors and pure red cell aplasia (PRCA).

PRCA is a rare but severe form of anaemia characterised by substantial reduction in red blood cell precursors while platelet and neutrophil counts are normal. PRCA should be suspected if a patient has been on previously effective ESA therapy for at least three months and there is sudden and severe unexplained fall in haemoglobin despite continuing treatment with the ESA. However, most PRCA cases have been reported in patients receiving Eprex by the subcutaneous route, for which it is no longer licensed. PRCA can be fatal and is often incurable, so ESA therapy should be stopped at the earliest indication that there could be a problem.

Conclusion

A decade ago, ESAs were a specialist product used cautiously in a minority of patients with CKD. Today, target haemoglobins are being reached in the majority of dialysing patients aided by widespread ESA and intravenous iron use.

Target haemoglobins are rising with the evidence base but there are still problems ensuring ESA availability in pre-dialysis populations to facilitate early and effective correction of renal anaemia.

We hope that the NICE clinical guideline for renal anaemia will not only resolve discrepancies between the EBPG and RAS but also ensure that all patients requiring ESAs receive them in the appropriate doses.

References

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