Managing the anaemia of chronic kidney disease

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Summary

Anaemia is a common manifestation of chronic kidney disease, especially when the glomerular filtration rate falls below 30 mL/min. It is important to exclude other causes of anaemia such as iron and other haematinic deficiencies, chronic inflammation, malignancy and drugs. After reversible causes of anaemia are excluded, supplementary erythropoietin (epoetin) can be considered when the patient's haemoglobin concentration falls below 100 g/L. Patients treated with epoetin often require supplements of oral or intravenous iron to maintain adequate iron stores during the correction and the maintenance phases of management. The main adverse effect of epoetin use is the development or worsening of hypertension. Care must also be taken not to overshoot the target haemoglobin of 110–120 g/L, as this can be associated with a prothrombotic tendency.

Key words: darbepoetin alfa, epoetin alfa, epoetin beta, erythropoietin, iron.

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Introduction

Erythropoietin is a hormone made predominantly within the peritubular cells of the kidney. It acts on the bone marrow, stimulating erythropoiesis. Erythropoietin also controls apoptosis (programmed cell death) of mature red blood cells. Renal disease reduces erythropoietin production.

The management of anaemia in chronic kidney disease has been revolutionised by the development of recombinant human erythropoietin (epoetin).[1] Many of the symptoms that had been ascribed to chronic kidney disease such as fatigue, lethargy, somnolence and shortness of breath, which all impact unfavourably on quality of life, were resolved or markedly improved when anaemia was corrected.[2] Before the development of epoetin, uraemic anaemia was managed by recurrent blood transfusions, with the risk of iron overload and viral infection (hepatitis B and C and HIV).

Uraemic anaemia

Although uraemic anaemia can be present when the glomerular filtration rate is above 30 mL/min, it is more prevalent when the rate falls below 30 mL/min (stages four and five chronic kidney disease). Patients with diabetic nephropathy or analgesic nephropathy (who took Bex, Vincent's or APC powders during the 1950s and 1960s) tend to be more anaemic than patients with other causes of chronic kidney disease. In contrast, patients with adult-onset polycystic kidney disease often maintain their haemoglobin concentrations as renal failure progresses.

Uraemic anaemia is characterised by relative erythropoietin deficiency. Chronic inflammation or infection, malignancy and hyperparathyroidism always need to be considered, but iron deficiency is the most common cause of reversible anaemia in patients with chronic kidney disease. Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers may reduce endogenous erythropoietin levels and contribute to anaemia in these patients. However, these effects are outweighed by their renoprotective benefits.

Iron deficiency is common in chronic kidney disease because of the widespread use of antiplatelet drugs (aspirin and clopidogrel), and a possible uraemic platelet defect, enhancing gastrointestinal blood loss.[3] Endoscopy should be considered to exclude gastrointestinal lesions. Haemodialysis patients are also exposed to heparin at least three times per week to prevent clotting on dialysis and a certain amount of blood is lost in the artificial kidney during each haemodialysis session.

Diagnosis of iron deficiency

If the patient has a low haemoglobin, iron studies are indicated. Serum ferritin is a marker of iron stores but can be elevated as an acute phase reactant, similar to C-reactive protein and erythrocyte sedimentation rate. Transferrin saturation reflects iron availability in the bone marrow. Both measurements are needed to assess iron status accurately. Serum iron is subject to diurnal variations in concentration and is not a useful marker of iron status in chronic kidney disease.

There is a chronic inflammatory state in patients with chronic kidney disease so the normal ranges for serum ferritin and transferrin saturation do not apply. Absolute iron deficiency cannot be excluded unless the ferritin is greater than 100 microgram/L or the transferrin saturation greater than 20%.

Treatment of iron deficiency

In patients who do not require dialysis, iron deficiency is managed with oral iron. The main adverse effects from oral iron include diarrhoea or other gastrointestinal upsets. The only oral iron tablets subsidised by the Pharmaceutical Benefits Scheme (PBS) are iron fumarate with folic acid. Some patients cannot tolerate oral iron and require admission for an intravenous infusion of iron polymaltose (500 mg). Iron polymaltose should not be injected intramuscularly because of the risk of tattoo or neuropraxia. Iron sucrose (100 mg) may be administered by slow intravenous injection.

When is treatment with supplementary epoetin considered?

If the patient does not respond to iron, and other causes of anaemia have been excluded, epoetin can be considered. It is expensive, but the PBS subsidises supplementary epoetin when the patient's haemoglobin concentration falls below 100 g/L. However, this subsidy does not consider comorbidities. Tailoring the use of epoetin to patients' underlying comorbidities makes sense because, for example, patients with chronic obstructive pulmonary disease would have higher baseline haemoglobins than the general population.

The target haemoglobin values have been studied in patients who have haemodialysis and in those who do not. The results have been disappointing when the target haemoglobin has been greater than 130 g/L.[4,5] Higher haemoglobin concentrations are associated with an increased risk of thrombotic events such as clotting in the arteriovenous fistulae used for haemodialysis access. These trials have led expert groups to recommend a target haemoglobin of 110–120 g/L for most patients.[6] Nevertheless, some prescribers may individualise epoetin dosages to achieve higher haemoglobin concentrations according to the patient's background functional status and other illnesses. Iron therapy continues, if required, depending on the results of blood tests.

Which supplementary epoetins are available?

Since the original epoetin alfa was released, there have been different molecular modifications including increased numbers of sialic acid residues, carbohydrate moieties or pegylation. These modifications increase the half-life of the epoetins and reduce the dosage frequency. All currently available epoetins correct anaemia to the same extent. The choice is dictated by the preferred frequency and route of administration (subcutaneous or intravenous).

All epoetins are subject to degradation if not refrigerated. Care must be taken when transporting epoetin from hospital or community pharmacies to the patient's home.

Epoetin alfa

This epoetin was released onto the Australian market in 1989. It has been extensively studied in trials since then. Originally it was given three times per week, but can be extended to weekly administration. Several years ago over 200 patients worldwide developed pure red cell aplasia secondary to the development of anti-erythropoietin antibodies. This manifested as severe transfusion dependent anaemia because the injected epoetin and any native erythropoietin were destroyed by these antibodies.

Epoetin beta

This epoetin has a similar pharmacological profile to epoetin alfa. Recently it has been shown to be less painful than darbepoetin alfa when injected subcutaneously.[7]

Darbepoetin alfa

This product has a much longer duration of action than the epoetins. The dosing schedule can be extended to monthly administration during the maintenance phase in patients who do not need dialysis. Whether the drug is administered intravenously or subcutaneously makes no difference to its efficacy in maintaining haemoglobin concentrations.

Methoxy polyethylene glycol-epoetin beta

This product has not as yet been released in Australia. It is a pegylated epoetin with a different mode of receptor activation. This further extends the dosing interval so that it can be administered monthly during either the correction or maintenance phase irrespective of whether or not the patient is having dialysis.

Biosimilar epoetin alfa

A biosimilar is a product which is similar to a biological medicine that has already been approved by the regulatory agencies but whose patent has typically expired. Biopharmaceuticals are far more complex than traditional chemical drugs in their structure, methods of production and modes of action. Biosimilar products are therefore similar but not identical to the innovator product. This is in contrast to generic medicines, which have the same chemical structure as the original medication. Biosimilar epoetins have been released in Europe and other countries now that the original patents have expired.[8] These drugs are produced with more modern production techniques than the innovator products and so may result in lower prices.

Other drugs

There are multiple new drugs currently under development or in clinical trials. These are peptides which stimulate the erythropoietin receptor through different mechanisms.

Hematide has an amino acid sequence that is unrelated to erythropoietin or to any other known naturally-occurring human proteins. It should therefore not cause pure red cell aplasia, the haematological disorder that can be induced by treatment with

other erythropoiesis stimulating agents. Its advantages include monthly administration, relatively uncomplicated chemical synthesis, greater stability than currently marketed products, and storage at room temperature.

What monitoring needs to be undertaken?

During the correction phase of anaemia, blood pressure should be monitored monthly and the haemoglobin concentration every 4–6 weeks. Hypertension is associated with a rapid rise in haemoglobin from baseline so the target rate of rise is 10 g/L/month. Iron studies should be checked at least once every two months, but this recommended frequency of monitoring has not been subject to clinical trial verification. Consultation with nephrology services is required during the correction phase, but monitoring of haemoglobin in the maintenance phase is often undertaken by general practitioners. In this setting, the frequency of haemoglobin monitoring can be extended to every 2–3 months, with iron studies every three months.

Conclusion

Anaemia is common in patients with chronic kidney disease. Other causes of anaemia should be excluded. Iron deficiency should be corrected, but if the haemoglobin falls below 100 g/L, treatment with a recombinant epoetin should be considered. This will correct the uraemic anaemia and maintenance therapy will be required once the target haemoglobin has been achieved. If epoetin is stopped, the haemoglobin falls back towards baseline. Correcting the anaemia can improve the patient's quality of life.

References

1. Winearls CG, Oliver DO, Pippard MJ, Reid C, Downing MR, Cotes PM. Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. Lancet 1986;2:1175-8.
2. Harris DC, Chapman JR, Stewart JH, Lawrence S, Roger SD. Low dose erythropoietin in maintenance haemodialysis: improvement in quality of life and reduction in true cost of haemodialysis. Aust N Z J Med 1991;21:693-700.
3. Roger S. Haematological targets: Iron. The CARI Guidelines. 2005. www.cari.org.au/DIALYSIS_bht_published/Iron.pdf [cited 2009 Sep 4]
4. Drüeke TB, Locatelli F, Clyne N, Eckhardt KU, Macdougall IC, Tsakiris D, et al; CREATE Investigators. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med 2006;355:2071-84.
5. Singh AK, Szczech L, Tang KL, Barnhardt H, Sapp S, Wolfson M, et al; CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006;355:2085-98.
6. McMahon L. Haematological targets: Haemoglobin. The CARI Guidelines. 2008. www.cari.org.au/DIALYSIS_bht_published/Haemoglobin_Aug_2008.pdf [cited 2009 Sep 4]
7. Roger SD, Suranyi MG, Walker RG; COMFORT study group. A randomised, cross-over study comparing injection site pain with subcutaneous epoetin beta and subcutaneous darbepoetin alfa in patients with chronic kidney disease. Curr Med Res Opin 2008;24:2181-7.
8. Roger SD, Mikhail A. Biosimilars: opportunity or cause for concern? J Pharm Pharm Sci 2007;10:405-10.

Dr Roger has served on advisory boards/speakers bureaus for Janssen-Cilag, Hoffman-La Roche, Amgen and Vifor. In addition, he has undertaken clinical trials in anaemia/iron management for Takida, Sandoz and the above companies.

Self-test questions

The following statements are either true or false
(answers on page 143)

3. Serum ferritin concentrations may be increased by chronic kidney disease.
4. Iron deficiency in patients with chronic kidney disease is due to erythropoietin deficiency.