The introduction of epoetin beta to Australia

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Abstract

The purpose of this review is to describe the relevance of the introduction of epoetin beta to the management of renal anaemia in Australia. Epoetin beta became available in Australia in May 2006. Like epoetin alfa and darbepoetin alfa, epoetin beta is reimbursed by the Australian Pharmaceutical Benefits Scheme (PBS) for the treatment of anaemia in patients with chronic kidney disease. All agents are effective in correcting and maintaining haemoglobin levels in patients with renal anaemia. Differences between the erythropoiesis-stimulating agents such as injection site pain, stability, dosing interval and hypersensitivity to medication may cause preference for one agent over another. Nurses should be aware of these differences for best patient outcomes.

Key Words
epoetin beta, anaemia, chronic kidney disease

What is epoetin beta?

Epoetin beta is a recombinant erythropoietin beta concentrate that has been marketed since 1990 in some parts of Europe. Epoetin beta was made available in Australia in May 2006 following the resolution of patent issues.

What is epoetin beta used for?

Like epoetin alfa and darbepoetin alfa, epoetin beta is indicated for the treatment of anaemia in pre-dialysis, haemodialysis, and peritoneal dialysis patients. Treatment with epoetin beta produces a dose-dependent increase in reticulocyte count, haematocrit and haemoglobin, and reduces the need for packed red blood cell transfusions in patients with renal anaemia (Bommer et al., 1988; Bennett, 1991). Epoetin beta also maintains haematocrit and haemoglobin levels for long-term treatment of anaemia (Bommer et al., 1988). Epoetin beta is also used in pre-donation programs to reduce the need for homologous blood, to prevent anaemia in premature infants, and to reduce the need for transfusion in patients with non-myeloid malignancies (NeoRecormon Product Information, 2005).

How is epoetin beta administered?

Epoetin beta has a convenient dosing schedule and can be administered subcutaneously once weekly for correction and maintenance. Patients stable with once-weekly dosing may be reduced to once-fortnightly dosing (NeoRecormon Product Information, 2005; Mirescu et al., 2006). With intravenous administration, three-times per week administration is recommended (NeoRecormon Product Information, 2005).

How is epoetin beta subsidised in Australia?

Epoetin beta is subsidised by the PBS on the S100 scheme for "treatment of anaemia requiring transfusion, defined as a haemoglobin level of less than 100 g per L, where intrinsic renal disease, as assessed by a nephrologist, is the primary cause of the anaemia" (Schedule of Pharmaceutical Benefits, 2007).

How does epoetin beta compare to other currently available erythropoiesis-stimulating agents?

Epoetin beta and the other currently available erythropoiesis-stimulating agents are produced by a complex manufacturing process. Slight changes in this process produce different molecules with different pharmacokinetic and pharmacodynamic profiles (Roger, 2006). Epoetin beta and epoetin

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alfa are recombinant human isoforms, whereas darbepoetin alfa is produced by site-directed mutagenesis.

The currently available erythropoiesis-stimulating agents have similar efficacy profiles (Aranesp Product Information, 2006; Eprex Product Information 2005; NeoRecormon Product Information, 2005) but differ in other characteristics, particularly those affected by formulation (i.e. tolerability, stability and prevalence of PRCA). A retrospective comparison of the use of epoetin alfa and darbepoetin alfa in Australian haemodialysis patients found there were slight differences in haematological parameters in patients receiving epoetin alfa compared with patients receiving darbepoetin alfa, although the clinical relevance of these small differences is uncertain (Pussel & Walker, 2007).

Possible reasons for switching a patient between erythropoiesis-stimulating agents may include patient preference, injection site pain, hypersensitivity to one of the erythropoiesis-stimulating agents, stability/storage, dosing interval, lack of response to one of the erythropoiesis-stimulating agents and the support provided by the manufacturer. To date, most cross-over studies have been conducted to determine non-inferiority of erythropoietic agents, and there is a lack of published data on the most common reasons for switching patients in the clinical practice setting.

How does the efficacy of the erythropoiesis-stimulating agents compare?

There is also a lack of data directly comparing the efficacy of the currently available erythropoiesis-stimulating agents. In more than 16 years of clinical experience with epoetin beta and epoetin alfa there have been no reports of a significant difference in the efficacy of these agents in treating renal anaemia. In trials establishing the efficacy of darbepoetin alfa in treating renal anaemia, comparison was made to either epoetin alfa alone (Locatelli et al., 2001; Nissenson et al., 2002) or epoetin alfa and epoetin beta, as recombinant human erythropoietin (rHuEPO) (Vanrenterghem et al., 2002; Locatelli et al., 2003). In all trials, darbepoetin alfa was demonstrated to be equivalent to recombinant human erythropoietin in the correction and maintenance of target haemoglobin.

Which treatment do patients prefer?

The issue of injection site pain is of genuine concern to patients using sub-cutaneous injections. Therefore it is of interest that studies have reported no difference in pain between epoetin beta and saline (Frenken et al., 1991; Veys et al., 1998; Coffier et al., 2005; Choukroun et al., 2005). In contrast, with the early use of epoetin alfa and epoetin beta several studies noted that epoetin alfa was more painful when injected subcutaneously than epoetin beta (Frenken et al., 1991; Granolleras et al., 1991;Veys et al., 1992;Veys et al., 1998). It should be noted that a different epoetin alfa formulation was used than the one that is currently available in Australia.

A high rate of injection pain has been reported in patients treated with subcutaneous darbepoetin alfa (Macdougall et al., 2003). In this study 30% of patients receiving subcutaneous darbepoetin alfa reported injection site pain. A randomised, crossover study reported a higher rate of injection site pain with darbepoetin alfa than epoetin (Vanrengterghem et al., 2002). A smaller study of 13 patients (aged 3-22 years) with end stage renal disease reported more intense immediate injection pain with darbepoetin alfa than with epoetin beta (median verbal pain scores, 5.4±1 versus 2.3±0.6, p=0.02; Schmitt et al., 2006). This was consistent with the perception of pain experienced by the patient as assessed by the caregiving nurse (4.4±1 versus 2.2±0.6, p = 0.02). In healthy adult volunteers, patients experienced significantly more pain immediately after injection with darbepoetin alfa 2.9 (95% CI: 2.1-4.0) than epoetin beta 1.2 (95% CI: 0.7-2.0) as measured on the Visual Analogue Scale (Coffier et al., 2005; Choukroun et al., 2005). The COMFORT study is currently investigating this in Australian renal anaemia patients and the results are awaited.

How do the safety profiles compare?

Epoetin beta, epoetin alfa, and darbepoetin alfa have very similar safety profiles as described in the Product Information for each product. Pure red cell aplasia is a rare but serious side effect associated with all three products. Unlike epoetin alfa, the rate of pure red cell aplasia associated with epoetin beta has remained constant at similar levels to background rates of non anti-erythropoietin medicated pure red cell aplasia (Macdougall, 2004; Boven et al., 2005).

How does the stability of the agents compare?

As a result of epoetin beta's formulation it may be removed from refrigerated storage for up to 3 days at room temperature (25°C) (NeoRecormon Product Information, 2005). In comparison, epoetin alfa should be stored at 2-8°C (Eprex Product Information, 2005). darbepoetin alfa may be stored outside the recommended temperature range of 2-8°C for up to 2 days without compromising the activity of the agent (Aranesp Product

Information, 2006). The stability of epoetin beta and darbepoetin alfa means that the medication can be allowed to reach room temperature prior to use. It is possible that injection of the medication at room temperature may be more comfortable for patients than injection of cold medication although this has not been confirmed. The stability of epoetin beta may also make it more convenient for rural patients and patients going on holiday as they can transport small amounts of the medication without having to ensure that it remains between 2-8^{o}C.

Discussion

The ability to use flexible regimens may be an important consideration in terms of convenience for patients and compliance of the patients to medication. For example, epoetin beta can be administered subcutaneously as a maintenance dose once a week or once every two weeks. (NeoRecormon Product Information, 2005; Mircescu et al., 2006). Patients may prefer once every two week dosing although it may be easier for them to comply with their dosing regimen if they are dosed once a week.

I present the following case study of ours that provides an example of how epoetin beta is being incorporated into clinical practice in Australia. A 61-year-old female with symptomatic anaemia secondary to chronic renal failure was administered subcutaneous darbepoetin alfa 60 μg fortnightly for six months. The patient had been receiving peritoneal dialysis therapy for more than 12 months and her haemoglobin levels had been maintained at approximately 125 g/L. The patient was switched to epoetin beta at 6000 IU once-weekly (based on a 1:200 conversion factor). During the initial switching of the medication, the patient informed the nursing staff that her level of injection pain was reduced. She stated "It doesn't hurt and no pain at all. It was sore with the old one, a bit sore". Follow-up haemoglobin levels after two months of therapy were maintained at approximately 128 g/L with no adverse effects.

What does the future hold for treatment of renal anaemia?

There are many agents in development for the treatment of renal anaemia (Macdougall and Eckardt, 2006). The next agent that is likely to become available is an erythropoiesis-stimulating agent called a continuous erythropoietin receptor activator (CERA), which is currently being tested in Phase III trials. CERA has a half-life of approximately 130 hours and phase II results suggest that this agent can be used at dosing intervals of up to once a month and still effectively control and maintain haemoglobin levels (Macdougall and Eckardt, 2006).

Conclusion

The introduction of epoetin beta to Australia provides healthcare professionals with another effective treatment in the management of renal anaemia. The flexible dosing of epoetin beta allows healthcare professionals the option of subcutaneous once-weekly or once-fortnightly subcutaneous dosing with the advantage of minimal injection site pain. The three erythropoiesis-stimulating agents currently available in Australia are effective in treating renal anaemia. Differences such as tolerability, stability, hypersensitivity, and lack of response are possible reasons to switch between erythropoiesis-stimulating agents. In the future it is likely that other agents will be introduced to Australia, further changing the landscape of anaemia management.

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