Erythropoietic proteins and antibody-mediated pure red cell aplasia: a potential role for micelles

Sir,

In a recent edition of NDT, Locatelli et al. [1] provided a useful review of the chronology and potential causes of anti-erythropoietin antibody-mediated pure red cell aplasia (PRCA) with erythropoiesis-stimulating agents, together with current actions and recommendations. The authors note the potential causal link between a change in the formulation of Eprex® (epoetin alfa), where the stabilizer human serum albumin was replaced with polysorbate 80 and glycine, and the recent upsurge in PRCA cases associated with its use [2]. However, a mechanism for how this formulation change breaks the immune tolerance to erythropoietin was not given.

In principle, two main mechanisms exist by which B cell tolerance to self antigens can be broken. One way of breaking tolerance is to present the self antigens in combination with a danger signal, such as denatured protein or endotoxins. The most potent way to induce antibodies to self antigens is to present the self antigens in highly structured arrays that resemble viral capsid-like structures. Several potential causes of antibody induction with Eprex have been put forward, including the presence of leached contaminants from the rubber stoppers of pre-filled syringes or the silicon oil used as a lubricant, which may act as ‘danger signals’.

We have shown recently the presence of surfactant molecule aggregations (otherwise known as micelles) in the Eprex formulation, which are caused by the high concentration of polysorbate 80. We have also shown that epoetin alfa is associated with these micelles, which may lead to the formation of structures with repeated epoetin antigens. These, in turn, may be presented at the surface of the micelles and break B cell tolerance. We employed gel permeation chromatography (GPC) and enzyme-linked immunosorbent assay (ELISA) to determine whether samples of Eprex (epoetin alfa) and NeoRecormon® (epoetin beta) formulations contained micelles and how much epoetin was micelle-associated [3]. The critical micelle concentration (CMC) is the concentration of a surfactant at which an appreciable number of micelles are formed, and CMCs for polysorbates 20 and 80 have been calculated previously [4]. Notably, Eprex contains 0.03% (w/v) Tween (polysorbate) 80, around 20 times its CMC; in contrast, NeoRecormon contains 0.01% (w/v) Tween 20, only approximately 1.5 times its CMC.

GPC analysis confirmed that the Eprex formulation contained micelles of polysorbate 80, while no micelles were detected with NeoRecormon. Subsequent analysis of the GPC fractions by ELISA demonstrated that with the Eprex samples, small amounts of epoetin were co-eluted with the polysorbate 80 micelles. No such co-elution was seen with NeoRecormon. The findings suggest that not only does the Eprex formulation contain polysorbate 80 micelles, but also that epoetin alfa molecules are solubilized in or attached to these micelles.

Micelle-associated epoetin is, therefore, a potential risk factor for immunogenicity in anaemic patients, and further investigation utilizing animal models may provide additional relevant data.

Conflict of interest statement. H.S. has participated in meetings and publications sponsored by Amgen, the makers of darbepoetin (Aranesp®); Johnson and Johnson, the makers of epoetin-alpha (Eprex®); and F. Hoffmann-La Roche, the makers of epoetin-beta (NeoRecormon®).

Central Laboratory Animal Institute
Huub Schellekens
and Department of Innovation Studies
Utrecht University
Utrecht, the Netherlands
Email: huubs@xs4all.nl

Managing refractory uraemic pericarditis with colchicine

Sir,

Pericarditis is a complication of end-stage renal disease (ESRD), still occurring in 20% of uraemic patients before and at the initiation of haemodialysis [1]. Multiple factors contribute to the appearance of uraemic pericarditis, which responds readily to treatment and has a good prognosis in the majority of cases. We present a patient with ‘refractory uraemic pericarditis’ who ultimately responded to colchicine. The use of colchicine in uraemic patients with pericarditis has not been reported previously.

A 48-year-old woman, suffering from ESRD due to autosomal dominant polycystic kidney disease, attended our clinic in August 2000. She manifested tachycardia and deep heart tones without fever, dyspnoea, thoracic pain or cough. Laboratory tests were compatible with ESRD. There was no leukocytosis. Chest X-ray, electrocardiogram and heart ultrason sound revealed a large amount of pericardial effusion (anterior wall, 9 mm; posterior wall, 17 mm), diastolic dysfunction and hypertension of the left ventricle; the ejection fraction remained within a satisfactory range (65%). The patient was enrolled in daily 3 h haemodialysis sessions without anticoagulation. A week later, a new ultrasound exhibited persistent pericardial effusion (anterior wall, 7 mm; posterior wall, 15 mm). Moreover, after 3 weeks of intensive dialysis, a progression of the effusion was noticed (anterior wall, 12.4 mm; posterior wall, 21.1 mm), while the ejection fraction remained stable. The patient’s condition was also...
stable, except for a mild tachycardia. Because of the progression, daily haemodialysis was continued for a further 2 weeks, during which a detailed search for accompanying diseases was completed, with negative results [white blood cells = 6000/mm³, anti-netutrophil; antibody (−), anti-DNA (−), C3 = 1.531 g/l, C4 = 0.42 g/l, erythrocyte sedimentation rate = 98 mm, C-reactive protein = 12.8 g/l, fibrinogen = 5.27 g/l, etc]. While the adequacy of dialysis was reconfirmed, the pericardial effusion did not change. Methylprednisolone at a dose of 40 mg/day was added, and a month later we noticed a moderate reduction of the effusion (anterior wall, 8.4 mm; posterior wall, 13.1 mm). The administration of methylprednisolone was tapered over 2 months to full cessation. However, 1 month after its discontinuation (6 months after the initiation of dialysis), a new increase in pericardial effusion was observed (anterior wall, 15 mm; posterior wall, 16 mm). The patient received a new course of steroid (1 mg/kg body weight), but a month later pericardial effusion had progressed further. Since the patient remained haemodynamically stable, the surgeon’s opinion was against intervention.

The type of surgical procedure utilized for cardiac tamponade is usually determined by local experience and by the condition of the patient. Acute cardiac tamponade with circulatory collapse should be treated with pericardiosentesis. On the other hand, pericardiocentesis is not recommended for effusions that do not produce circulatory compromise. The morbidity and the potential of mortality (due, for example, to right ventricular laceration) in this setting are not insignificant. In the literature, there are two justifying indications for pericardiotomy or pericardectomy: (i) any recurrence (and certainly more than one recurrence) if accompanied by cardiac tamponade; and (ii) if a recurrence is manifested principally by persistent pain, despite a trial of intensive medical treatment and evidence of serious steroid toxicity [2,3]. None of the above conditions were met in the present case. Our review of the literature led us to the administration of colchicine, 2 mg per day for 5 weeks, followed by 1 mg and then 0.5 mg per day, for a total of 18 months. Steroids were gradually tapered and finally stopped after 6 weeks.

Seven weeks after the initiation of colchicine, the pericardial effusion was diminished (anterior wall, 13.5 mm; posterior wall, 15 mm). Further reduction of the pericardial effusion was noticed 4 months after the initiation of colchicine (anterior wall, 7.6 mm; posterior wall, 9.7 mm); 6 months later, the remaining effusion did not exceed 5–6 mm. Thirty-six months later, the patient remains free of pericarditis.

In this rare case of resistant pericarditis, we used colchicine after the failure of intensive dialysis and steroids administered for an adequate time. In a review of the available data, Adler et al. reported numerous cases of non-uraemic recurrent pericarditis treated effectively with colchicine [4]. Colchicine is considered to exert its action through the inhibition of nucleated blood cell function and motility by blocking intracytoplasmic microtubule polymerization. This occurs independently of the underlying inflammatory process [5]. Some authors recommend its use even as an initial treatment of acute pericarditis. Satisfactory results are obtained with sufficient doses for an adequate time [6]. The administration of small doses of colchicine, as an alternative treatment of refractory pericarditis, is included in guidelines of the World Heart Federation [7], but its use in uraemic patients has not been reported in the literature. In the present case of intractable pericardial effusion, colchicine proved to be helpful, efficient and safe.

Conflict of interest statement. None declared.

Renal Department 2nd Hospital of IKA Thessaloniki Greece E-mail: renalika@the.forthnet.gr

Sofia Spaia Stavros Patsalas Argiri Agelou Charouli Theodoroglou Nikolao Askepidis Michailia Pazarakoglou Hizaklis Ioannidis

Corticosteroid and tamoxifen therapy in sclerosing encapsulating peritonitis in a patient on continuous ambulatory peritoneal dialysis

Sir,
Sclerosing encapsulating peritonitis (SEP) is a clinical syndrome associated with ileus symptoms and irreversible sclerosis of the peritoneal membrane [1–4]. There is no evidence-based therapy for SEP [2]. Current suggestions include anti-inflammatory and immuno-suppressive drugs [2–7]. We report here a case of SEP, presenting with refractory peritonitis and severe abdominal symptoms.

Case. A 29-year-old woman developed end-stage renal disease secondary to reflux nephropathy in 1992. She was started on haemodialysis and was subsequently transferred to continuous ambulatory peritoneal dialysis. She was hospitalized with high fever, abdominal pain and turbid dialysate. Despite vancomycin and amikacin, she remained unwell. She was then switched back to haemodialysis. Abdominal tomography was diagnostic for SEP showing enlarged small bowel loops with an increase of peritoneal thickness. She underwent laparotomy and biopsies were taken from the peritoneum. Pathological examination confirmed the clinical diagnosis of SEP. The patient was given tamoxifen 10 mg/day and prednisolone 0.5 mg/kg/day. Her symptoms improved gradually over 2 months with an increase of serum albumin and body weight.

Chlorhexidine gluconate in alcohol, a cleanser for the peritoneal dialysis catheter, is responsible for the development of SEP [1,6,8]. Glucose-based dialysis solutions, recurrent peritonitis attacks, plasticizers and particles may also be aetiological factors [6]. The diagnosis of SEP is generally made on a peritoneal biopsy. The mortality rate was up to

2. Shabetai R. Recurrent pericarditis Copyright© 2003 UpToDate® www.uptodate.com (800) 998-6374 (781) 237-4788

DOI: 10.1093/ndt/gfh407