Full Dapsone Dose Made Possible by Control of Anaemia with Darbepoetin-alpha

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Sir,

Dapsone is a first-line immunosuppressive treatment for many inflammatory diseases. Tolerance of the drug at higher doses is usually determined by its haematological side-effects, *viz* haemolysis and methaemoglobinaemia (1). These adverse effects are due entirely to hepatic N-hydroxylation of the drug to a hydroxylamine metabolite, some of which escapes from the liver and rapidly enters red cells (1). We describe here a case in which dapsone-induced haemolysis was treated with darbepoetin-alpha.

CASE REPORT

An 84-year-old man presented who had had symblepharon and entropion that had required multiple operations, but with poor results. He also had oral mucosal lesions and desquamative gingivitis, both of which affected his sleep and eating habits. His dentist referred him to us because he noticed a lesion in the skin. Linear IgA disease was suspected and confirmed by typical histopathological changes showing subepidermal blistering with predominant neutrophilic infiltrate in the upper dermis and immunofluorescent staining showing linear deposition of IgA at the basal membrane zone. He was initiated cautiously on 25 mg of dapsone daily, due to his age. In a few days his haemoglobin level fell from 121 g/l to 107 g/l. There was no therapeutic effect and the dose was increased to 50 mg dapsone daily, but his haemoglobin level fell further, to 98 g/l. The patient became pale with cyanotic lips, but not icteric (total bilirubin 12 μmol/l, haptoglobin 2.07 g/l, se-lactate dehudrohenase (LDH) 266 U/l (ref. value 240–480 U/l), mean corpuscular volume (MCV) 98 fl, se-B12 375 pmol/l, erythrocyte folate 3596 nmol/l, se-iron 10 μmol/l and se-total iron binding capasity (TIBC) 52 μmol/l). He experienced severe tiredness and instability when walking, and the lesions improved only minimally on that dose. We reduced the dose to an average daily dose of 37.5 mg (alternating 50 mg one day and 25 mg the next) and the lesions became worse. In order to treat the anaemia, we considered darbepoetin-alpha which is a hyperglycosylated derivative of erythropoietin (2) with a three-fold longer terminal half-life (3). We administered 50 μg s.c. of darbepoetin-alpha weekly and gradually increased the dapsone to 150–200 mg daily, which was required to control the disease. Under these conditions his average haemoglobin level has been approximately 130 g/l during a 3-year follow-up without lesions. During that time, the total bilirubin has been normal (<25μmol/l) apart from an approximately 2-month period when he was weakly icteric with a total bilirubin of 28–30 μmol/l and classical routine blood testing values for haemolytic anaemia as follows: hemoglobin 117 g/l, MCV 108.9 fl, reticulocytes 3.2%, se-LDH 517 U/l, se-B12 286 pmol/l, erythrocyte folate 2653 nmol/l, se-iron 23 μmol/l and se-TIBC 47 μmol/l. Haptoglobin levels remained at 0.00 g/l throughout treatment with darbepoetin-alpha. No problems with methaemoglobinaemia were observed during treatment. Blood neutrophils and serum creatinine were within normal limits and were unaffected by the treatment.

DISCUSSION

Dapsone (4,4'-diaminodiphenyl sulphone) is known to suppress inflammatory conditions associated with neutrophils. At the cellular level it is considered to inhibit myeloperoxidase-catalysed reactions of the neutrophils (4). It has been postulated that the drug inhibits calcium-dependent functions of the neutrophils, including release of tissue-damaging oxidants and proteases in the affected skin (5), and that it inhibits the process by which neutrophils leave the circulation and migrate to lesional sites (6). Furthermore, it is thought to inhibit adherence of neutrophils to the basement membrane zone antibodies, possibly by direct effect on the antibodies (7). Dapsone is eliminated by oxidation predominantly by cytochrome P450 3A4 (8). It has been postulated that the oxidation is by myeloperoxidase to hydroxylamine, which may be responsible for the pharmacological effects as well as the side-effects of methaemoglobinaemia and haemolysis caused by the drug (9).

Control of anaemia with darbepoetin-alpha has been reported in association with cancer chemotherapy (10) Apart from that field, and to the best of our knowledge, this is the first time darbepoetin-alpha has been used successfully to control a drug-induced anaemia. It has, however, been discussed in the literature whether the drug may be effective in treating anti-viral induced anaemia (11). Darbepoetin-alpha has been used in the treatment of renal failure (12), to control anaemia due to inflammatory bowel disease (3) and in diabetes-induced anaemia (13).

Linear IgA disease is a rare acquired autoimmune bullous disorder. It has a variable course and may last for years, with spontaneous resolution in some cases. Reported remission rates range from 10% to 60% (14). When it is manifested simply as oropharyngeal ulceration and desquamative gingivitis, it may, unfortunately, result in a diagnostic and treatment delay (15). Long delay may result in a serious ophthalmological outcome, as the disease may lead to blindness. We suggest that physicians consider the option of controlling dapsone-induced anaemia with darbepoetin-alpha before considering treatment with stronger immunosuppressive medications with increased mortality rates. We feel that such a choice might have a trivial outcome in our case, considering the age of the patient.

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