Hemorrhagic cystitis following dexamethasone: Cyclophosphamide pulse therapy

Sir,

Cyclophosphamide was originally used as an anti-cancer drug; however, its uses have broadened and is now commonly used in many dermatologic disorders like bullous disorders, vasculitis and connective tissue disorders. Dexamethasone–cyclophosphamide pulse (DCP) therapy,[1] designed by Pasricha and Gupta for pemphigus was first used in 1981 with the aim of reducing the toxicity of corticosteroids and also achieve better therapeutic results. Dexamethasone–cyclophosphamide pulse therapy is used as first-line therapy in pemphigus in many centres in India. Hemorrhagic cystitis occurs in 5–10% of patients treated with cyclophosphamide and is believed to be caused by the metabolite acrolein.[2] Acrolein is toxic to the bladder epithelium and can lead to hemorrhagic cystitis. Mesna (is an acronym for 2 Mercapto Ethane Sulfonate Sodium [na]) is used therapeutically to reduce the incidence of hemorrhagic cystitis. Mesna assists to neutralize these metabolites by binding through its sulfhydryl-moieties, and also increases urinary excretion of cysteine.[3] Side effects of mesna include nausea, vomiting, headache, diarrhea and generalized weakness. We report a 73-year-old female with pemphigus who was controlled with standard DCP therapy. After receiving her seventh pulse (*phase 1 – total cumulative dose of 10.5 g of cyclophosphamide*), she presented with gross hematuria, dysuria and increased frequency of micturition. Her urine routine showed plenty of RBCs/high power field. Hemogram, renal parameters, bleeding time and clotting time were within normal limits. USG pelvis was normal. Urine culture was sterile. Hence a diagnosis of hemorrhagic cystitis secondary to cyclophosphamide was made. She was treated with 1 pint of normal saline followed by 2.5 l of oral fluids per day for 4 days. Tolterodine, a muscarinic receptor antagonist, was given to treat dysuria. Her symptoms subsided after a week. This is probably the first case report of hemorrhagic cystitis following DCP therapy.

Ballen *et al*.[4] reported 100 consecutive patients who underwent autologous or allogeneic bone-marrow transplantation and received high-dose cyclophosphamide with hyperhydration using 5% dextrose normal saline at the rate of 250 ml/h and furosemide with only two patients developing clinically significant hemorrhagic cystitis. Shepard *et al*.[5] compared mesna versus hyperhydration for the prevention of cyclophosphamide-induced hemorrhagic cystitis in bone-marrow transplantation and concluded that both mesna and hyperhydration were equally effective in preventing cyclophosphamide-induced hemorrhagic cystitis. The efficacy of hyperhydration or mesna in prevention of cyclophosphamide-induced hemorrhagic cystitis secondary to DCP therapy has not been evaluated. Since mesna is associated with side effects, we decided to use hyperhydration prophylactically to prevent hemorrhagic cystitis.

We have adapted a new protocol to prevent hemorrhagic cystitis.

Day 1: Dexamethasone 100 mg in 500 ml of 5% dextrose.
Day 2: Dexamethasone 100 mg in 500 ml of 5% dextrose was given followed by 500 mg of cyclophosphamide in 250 ml of 5% dextrose which is then followed by 500 ml of normal saline.
Day 3: Dexamethasone 100 mg in 500 ml of 5% dextrose.

Patients were also asked to take adequate oral fluids and frequently void urine. It can be argued that oral fluids alone would be adequate to prevent hemorrhagic cystitis; however, we found that patients admitted in bed were not taking adequate fluids in spite of being advised (personal observation).

We administered this revised form of DCP for 15 patients and found no signs of fluid overload. None of our patients had congestive cardiac failure or renal failure. We recommend this above modification of DCP to prevent cyclophosphamide-induced hemorrhagic cystitis.

C. R. Srinivas, C. Shanmuga Sekar, L. Somakumar

Department of Dermatology, PSG Hospitals, Coimbatore, India

Address for correspondence: Dr. C. Shanmuga Sekar, Department of Dermatology, PSG Hospitals, Peelamedu, Coimbatore - 641 004, Tamil Nadu, India
E-mail: drshannfun@sify.com

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