CASE REPORT

Water intoxication induced by low-dose cyclophosphamide in two patients with systemic lupus erythematosus

M Salido1,2, P Macarron2, C Hernández-García2, DP D’Cruz1, MA Khamashta1 and GRV Hughes1

1Lupus Research Unit, Rayne Institute, St Thomas’ Hospital, London UK; 2Service of Rheumatology, Hospital Clínico San Carlos, Madrid, Spain

Cyclophosphamide (CY) is an alkylating agent used to treat a variety of autoimmune disorders. Water intoxication is a well-known complication of high-dose intravenous (i.v.) CY, but is rare in patients treated with low dose i.v. CY. We describe two patients with lupus nephritis and water intoxication following low dose i.v. CY. The first patient was treated with oral prednisolone and azathioprine for eight weeks with inadequate response and persistent renal inflammatory activity. Eight hours after the first i.v. CY pulse she had a grand mal seizure. The second patient had WHO class III lupus nephritis, and after a single i.v. CY pulse developed vomiting, diarrhoea and grand mal seizures. They were both fluid-restricted and their serum sodium levels returned to normal. In conclusion, even at low doses i.v. CY may induce hyponatremia related to inappropriate antidiuretic hormone secretion. This potentially life-threatening complication of i.v. CY could be minimized by avoidance of overhydration following pulse i.v. CY. Lupus (2003) 12, 636–639.

Key words: cyclophosphamide; lupus nephritis; water intoxication

Introduction

Cyclophosphamide (CY) is an alkylating agent used extensively in the treatment of malignant and rheumatological disease. Its side effects include bone marrow depression, infection, alopecia, sterility, bladder malignancy, haemorrhagic cystitis and, when used in high doses, myocardial damage.1 Water intoxication following i.v. CY at lower doses is rarely described, although there are several reports of hyponatremia after high and moderate doses of i.v. CY.2–6 We found only three reports of hyponatremia following low doses of i.v. CY.1,7,8 We agree with Spital and Ristow8 that this complication is not widely appreciated in the rheumatology literature, particularly since low-dose i.v. CY is being used with increasing frequency in the treatment of rheumatological diseases. We report two patients with systemic lupus erythematosus (SLE) who developed severe water intoxication following administration of low doses of i.v. CY.

Case reports

Case 1

A 48-year old woman presented in 1998 with malar rashes, mouth ulcers and arthralgias. She had positive antinuclear, anti-double stranded DNA (anti-dsDNA) and antcardiolipin antibodies. Her SLE was treated with low-dose oral prednisolone, aspirin and chloroquine. When she was on 7.5 mg of prednisolone she flared with worsening joint and cutaneous lesions. Serum urea was 3.4 mmol/L, creatinine 64 μmol/L, serum albumin was 44.3 g/L and creatinine clearance 80 mL/min with 24-hour protein excretion of 2.7 g. The urinary sediment was active with haematuria, hyaline and granular casts. Serum electrolyte levels were normal. A percutaneous renal biopsy was not possible and her lupus nephritis was treated with oral prednisolone (1 mg/kg/day) and azathioprine (3 mg/kg/day) for eight weeks. Owing to inadequate response and persistent renal inflammatory activity she received a single bolus injection of i.v. CY 750 mg (12.5 mg/kg). She tolerated the CY well, and went home with instructions to drink at least 3 L of water a day to maintain hydration and minimize the risk of haemorrhagic cystitis. The patient became confused, disoriented and incoherent eight hours after CY administration, and had one generalized seizure 14
hours after therapy. On admission, she was in a postictal state and had two more grand mal seizures. Her blood pressure was normal and she was clinically euvoletic. Her initial serum sodium was 119 mmol/L, serum creatinine was 72 µmol/L, and 12 hours later, urine and plasma osmolalities were 255 mosm/kg and 468 mosm/kg, respectively. All other biochemistry and computed tomography (CT) brain scan were normal. She was treated with i.v. isotonic saline (0.9% NaCl) at 75 mL/h and water restriction. There were no further seizures. Her serum sodium gradually rose to 137 mmol/L and 141 mmol/L after 16 and 24 hours, respectively, and her mental status returned to normal. One month later, oral CY was initiated with good control of renal disease and no adverse effects.

Case 2

A 53-year-old woman was diagnosed with SLE and Sjögren’s syndrome 10 years ago and responded to hydroxychloroquine, aspirin and low-dose prednisolone. There was no previous evidence of renal tubular disease. Two years ago, mild proteinuria and haematuria was managed with a brief course of high-dose steroids (1 mg/kg/day) with good response. She later developed significant haematuria and proteinuria (1.03 g/day) with normal urea, electrolytes and serum creatinine but reduced serum albumin 25 g/dL. Renal biopsy showed WHO class III focal proliferative lupus nephritis with an associated mild focal tubulo-interstitial nephritis. NIH activity index was 6/24 and chronicity index was 4/12. She was given three 500 mg methylprednisolone pulses. One week later, she attended for the first pulse of i.v. CY 500 mg given with 200 mg of Mesna and Domperidone. She felt well after CY infusion, which had finished around 15.30 h. She took Mesna 400 mg at 18.00 h and at 22.00 h, and further domperidone at 22.00 h. About 10 minutes later (seven hours after the infusion), she had very severe vomiting and diarrhoea, and collapsed with several grand mal seizures. On admission her sodium was 119 mmol/L. Her blood pressure was 168/100 mmHg and her Glasgow coma score was 11/15, but without focal neurology. Her chest was clear and CT brain scan was normal. Urine analysis showed protein ++ and a small amount of blood. The plasma osmolality was 255 mosm/kg and the urine osmolality was 464 mosm/kg. She was fluid-restricted and her sodium subsequently rose to normal. She made a complete recovery. In retrospect, she reported that she had rapidly drunk 3 L of fluid in the two hours prior to the pulse of CY, thus increasing the risk of water intoxication. She has subsequently received six pulses of CY 500 mg without further complications. She is now well on methotrexate and has mild proteinuria with normal renal function.

Discussion

Severe hyponatremia has been reported in patients treated with high-dose i.v. CY (30–40 mg/kg).1-4 It has also rarely been seen in patients treated with moderate doses (20–30 mg/kg).1-4 To our knowledge only three cases of life-threatening water intoxication1,7,8 have been described following low-dose CY therapy (< 15 mg/kg). The data is summarized in Table 1. One patient with multiple myeloma received low-dose CY and indomethacin,1 another patient was treated with CY and prednisone7 and one received low-dose CY for peripheral sensory neuropathy secondary to Sjögren’s syndrome.8 Our two patients with lupus nephritis illustrate that life-threatening water intoxication may rapidly develop even after low-dose i.v. CY. We suspected i.v. CY as the cause of severe hyponatremia in our patients with SLE because no other cause was apparent. These patients had normal electrolytes and renal function, with no evidence of neurological or endocrine abnormalities prior to treatment with CY. Neither nausea and vomiting nor concomitant drug administration could be implicated in the water intolerance. Hyponatremia developed less than 20 hours after receiving i.v. CY, a time course similar to previous reported cases.1,4,6,8 In both patients, the ability to excrete water was soon normalized. It has been clearly demonstrated that CY transiently impairs the kidney’s ability to dilute the urine.2,4-6,9

In all reports of CY-induced water intoxication, the drug was given intravenously.1-4,6-8 Hyponatremia usually occurs 4–12 hours after the administration of CY, although sometimes not until 48 hours afterwards, and returns to normal in around 24 hours. The antidiuretic effect seems to be related to the appearance of an active alkylating metabolite of CY. There are various explanations for this. First, the half-life of CY in the blood has been estimated to be 6–7 hours,10,11 but the maximum antidiuretic effect occurs later, 10–14 hours after drug administration.

<table>
<thead>
<tr>
<th>Author</th>
<th>Dose of CY used (mg/kg)</th>
<th>Serum sodium (mmol/L)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Webberly, 1989</td>
<td>10</td>
<td>108</td>
<td>1</td>
</tr>
<tr>
<td>McCarron, 1995</td>
<td>10</td>
<td>116</td>
<td>7</td>
</tr>
<tr>
<td>Spital, 1997</td>
<td>&lt; 15</td>
<td>117</td>
<td>8</td>
</tr>
<tr>
<td>Our patients</td>
<td>12.5</td>
<td>119 (first case)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>500 mg</td>
<td>119 (second case)</td>
<td></td>
</tr>
</tbody>
</table>

CPM = cyclophosphamide.

Table 1: Published reports of hyponatremia after low-dose i.v. CY

Authors:

M Salido, et al.

Reference:

Lupus 2016

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Secondly, De Fronzo et al. observed a relationship between the appearance in the urine of an active alkylating metabolite of cyclophosphamide and the rise in urine osmolarity, the fall in urinary output and weight gain. Finally, CY itself is devoid of alkylating activity and must be activated by liver microsomes to form pharmacologically active metabolites.

The mechanism by which the active form of CY exerts an effect on urine concentrating ability has not been determined. Harlow et al. suggested a syndrome of inappropriate antidiuretic hormone secretion (SIADH). This hypothesis is corroborated by the postmortem examination performed on one patient who had received high-dose CY, demonstrating loss of Herring’s bodies and degranulation of various hypothalamic neurosecretory organelles. This metabolite could act indirectly by causing ADH release and this has been demonstrated with ifosfamide, a close structural analogue to CY. However, other studies have shown that monitored serum ADH levels have not altered significantly during treatment with CY. Therefore, although the clinical picture of CY-induced hyponatremia is typical of SIADH, this term is a misnomer. De Fronzo et al. believed that the occurrence of antidiuresis without altered glomerular filtration rate or urine sodium excretion is best explained by a direct effect of an alkylating metabolite of CY on the kidney resulting in enhanced permeability of the distal tubules to water. Further evidence of the possible site of interaction between CY and ADH comes from hypopituitary patients treated with CY who still develop water intoxication.

Impairment of water excretion by cyclophosphamide is relatively common, at least when higher doses are used. When moderate doses were given (750 mg/m²) water intolerance developed rapidly, but was usually subclinical. These observations suggest that while life-threatening acute hyponatremia after i.v. CY is infrequent, impaired water excretion is not. Spital and Ristow suspect that many patients may develop unrecognized hyponatremia following this therapy.

Acute hyponatremia causes cerebral oedema, which leads to a variety of signs and symptoms such as headache, nausea, altered mental status and seizures. It has the potential to induce permanent neurological injury or even death. Our patients had several generalized seizures that resolved immediately without permanent neurological injury following treatment with i.v. isotonic solution and water restriction.

CY does not have intrinsic renal toxicity, but the presence of renal failure or severe hypoalbuminemia could intensify the duration of the water-retention syndrome by prolonging the half-life of CY or its alkylating metabolites. Caution is thus necessary in patients with significant renal impairment and/or hypoalbuminemia. Simultaneous administration of NSAIDs such as indomethacin may also contribute to the acute water intoxication.

One factor that almost certainly may contribute to water intoxication is the general advice to patients to drink 2–3 L of fluid following i.v. CY to reduce the risk of haemorrhagic cystitis. The routine use of Mesna and lower doses of i.v. CY should reduce the need for vigorous hydration and so reduce the risk of water intoxication. Our own practice is to check renal function, electrolytes, serum albumin and full blood count on the day of i.v. CY administration and to advise patients to drink 1 L of fluid over and above their usual fluid intake in the following 24 hours. Care is taken to explain that rapid consumption of large fluid volumes should be avoided. In patients with significant renal impairment, severe hypoalbuminemia or tubulo-interstitial damage on renal biopsy, furosemide at the time of i.v. CY therapy may be considered. Furthermore, reconstituting CY in normal saline further reduces the risk of hyponatremia.

We have been using low-dose i.v. CY for the last 15 years and over 1000 pulses have been administered at St Thomas’ Hospital. These are the first patients in our respective units to suffer this rare complication. Low-dose i.v. CY is being used with increasing frequency in the treatment of autoimmune diseases. Although low-dose i.v. CY-induced water intolerance is usually subclinical, greater awareness of this potentially life-threatening complication of water intoxication may reduce the risk of its occurrence.

References


