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SHORT COMMUNICATION

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Increased urinary losses of carnitine during ifosfamide chemotherapy

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Abstract Chloroacetaldehyde and thiodiglycolic acid, two metabolites of ifosfamide, interfere with mitochondrial function and may sequester carnitine. Urinary excretion of carnitine was measured in five patients before and during a continuous infusion of ifosfamide over 5 days at a dose of 2.8–3.2 g/m^2 per day. The excretion of free and total carnitine increased from 85 ± 53 to 2697 ± 1393 μmol/day on the 1st day of chemotherapy and then gradually decreased. The average loss of carnitine during a chemotherapy cycle amounted to 8.5 mmol. The formation and excretion of esters of carnitine and metabolites of ifosfamide and/or a decreased renal tubular reabsorption could account for this marked loss, which might lead to symptomatic carnitine deficiency after several chemotherapy cycles.

Key words Urinary excretion · Carnitine · Ifosfamide

Introduction

As compared with other oxazaphosphorines, ifosfamide has a distinct profile of adverse side effects that can be attributed to metabolites [2]. Some of the adverse effects, such as the fatigue and the encephalopathy associated with the administration of high doses of ifosfamide, may be related to mitochondrial dysfunction as indicated by the glutaricaciduria that has been observed following ifosfamide treatment [5, 6]. Chloroacetaldehyde and thiodiglycolic acid, two metabolites of ifosfamide generated by dechlorethylation, interfere with mitochondrial function and may sequester carnitine [14, 15]. Consequently, ifosfamide therapy might result in a derangement of fatty acid oxidation and carnitine homeostasis. Therefore, the urinary excretion of carnitine was measured in patients treated with ifosfamide.

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Patients and methods

Five male patients (age 26–52 years) with advanced soft-tissue sarcoma were investigated. All gave informed consent to participate in the study, which had been approved by the local ethics committee. All patients had a creatinine clearance of >60 ml/min, transaminase levels of less than 2 times the upper limit of normal, a hemoglobin value of >10 g/l, a leukocyte count of $>3.5 \times 10^9$/l, and a thrombocyte count of $>100 \times 10^9$/l. The body mass index ranged from 17.7 to 24.9 kg/m^2 and the body weight, from 46 to 74 kg. The patients received a continuous infusion of ifosfamide at a dose of 2.8–3.2 g/m^2 per day over 5 days. Mesna was given together with ifosfamide by continuous infusion over the same period at a dose of 1.9–2.8 g/m^2, i.e., 80% of the dose of ifosfamide as determined on a weight-to-weight basis. The patients received intravenous fluids at a rate of 3 l/day for further reduction of the risk of the urotoxicity of ifosfamide. Urine was collected in 24-h portions on the day prior to chemotherapy and during chemotherapy. No episode of encephalopathy was observed. Urine was also collected for 24 h from six healthy subjects weighing between 65 and 76 kg.

Carnitine was measured colorimetrically before and after hydrolysis of carnitine esters using acetyl-CoA, 5,5′-dithiobis-(2-nitrobenzoic acid), and carnitine acetyl transferase [7]. To exclude the possible interference of mesna and ifosfamide and their metabolites with the determination of carnitine in urine, urine samples from patients receiving mesna and ifosfamide were spiked with known amounts of carnitine, and the carnitine concentration was measured. The resulting standard curves showed a parallel shift to standard curves of carnitine in buffer, indicating that ifosfamide and mesna, which is excreted in urine in the form of disulfides [2], do not interfere with the assay of carnitine.

The results are presented as mean values ± SEM. The data were analyzed by repeat-measure one-way analysis of variance, and subsequent comparison of the values recorded during chemotherapy with the baseline excretion of carnitine using Dunn's method.

Results

The urinary excretion of carnitine by the tumor patients prior to the infusion of ifosfamide (85 ± 53 μmol/day) was not significantly different from the excretion of

carnitine by six healthy subjects (94 ± 14 μmol/day). During the infusion of ifosfamide the urinary excretion of free and esterified carnitine increased markedly to 2697 ± 1393 μmol/day on day 1 of the chemotherapy cycle (Fig. 1). The excretion was elevated 10-fold on the day after cessation of the infusion of ifosfamide. During one chemotherapy cycle the patients lost 8.5 ± 3.1 mmol of carnitine.

Discussion

The administration of ifosfamide resulted in a marked increase in the urinary excretion of carnitine, which had been similar to that of healthy controls prior to chemotherapy. Several factors could have contributed to the loss of carnitine. First, two metabolites of ifosfamide, chloroacetaldehyde and thiodiglycolic acid, might have interfered with carnitine homeostasis. The oxidation product of chloroacetaldehyde, chloroacetic acid, sequesters carnitine as documented by the excretion of chloroacetylcarnitine in the urine of patients treated with ifosfamide [8]. Thiodiglycolic acid, which is excreted in large amounts by patients treated with ifosfamide, may interfere with mitochondrial function as do other thia fatty acids and dicarboxylic acids [11, 15]. Both chloroacetaldeyde and thiodiglycolic acid inhibit the oxidation of palmitic acid in intact rats, whereas the oxidation of octanoic acid and succinic acid, two substrates that are not dependent on carnitine for their metabolism, is not affected [13, 15]. Second, similar to the loss of carnitine observed following the administration of cisplatin, renal tubular damage might result in an increased urinary loss of carnitine [4, 12]. However, whereas renal injury is commonly associated with cisplatin, renal tubular damage is generally not a problem after ifosfamide administration, except in children [9, 10]. Considering the anorexia experienced by patients during a course of chemotherapy, an increase in the dietary intake of carnitine, which is an important determinant of its urinary excretion, can be excluded. Also, tissue destruction by the chemotherapy is unlikely to account for the loss of carnitine, since approximately 1 kg of tissue would have to be destroyed to account for the amount of carnitine excreted.

The total body content of carnitine in adults amounts to 50–100 mmol, most of it being localized in skeletal muscle [1]. During one chemotherapy cycle, patients lost approximately 10% of their carnitine stores. Together with the marginal carnitine stores present in some patients with advanced tumors [3], the observed loss might result in carnitine deficiency, which could be responsible for some of the symptoms associated with ifosfamide chemotherapy.

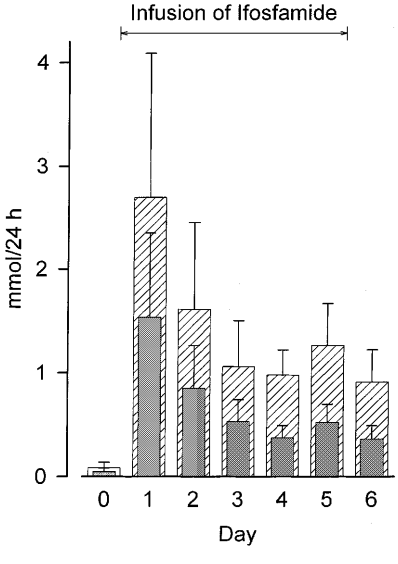

Fig. 1 Excretion of total carnitine (*hatched bars*) and free carnitine (*gray bars*) in the urine of five male patients receiving a continuous infusion of ifosfamide. The values determined on days 1–5 are significantly ($P < 0.05$) different from the baseline. Mean values ± SEM

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