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Fatigue and carnitine levels over multiple cycles of chemotherapy in children and adolescents

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A B S T R A C T

Purpose: Fatigue in childhood cancer is a pervasive and distressing symptom described as a "lack of energy". Carnitine is a micronutrient used to transport long chain fatty acids into muscle mitochondria. Some chemotherapy drugs interfere with the carnitine network. Both carnitine and fatigue relate to physical energy and may be influenced by chemotherapy. Using a repeated measures design, change in carnitine levels and change in fatigue in childhood cancer patients receiving ifosfamide, cisplatin, or doxorubicin were examined over multiple chemotherapy cycles. The influence of carnitine levels on fatigue was evaluated.

Methods and Sample: Fifty-eight patients, between ages 3 and 18 years, within two months from diagnosis and receiving cisplatin, doxorubicin, and/or ifosfamide chemotherapy drugs, participated. Measurements included carnitine plasma levels and self-reported fatigue using established child or adolescent fatigue scales and were collected during the 2nd cycle of chemotherapy, and repeated on alternating cycles up to cycle 8. The Parent Fatigue Scale was used for children under age 7.

Key Results: Total and free carnitine levels did not change significantly for the group. Fatigue decreased significantly in children age 7–12 ($p = 0.04$). Relationships between fatigue and carnitine were not significant.

Conclusions: Changes in carnitine plasma levels were not significant in this sample of patients. The carnitine levels remained within the reference values for children and were not associated with fatigue levels. School-age children may be more resilient to fatigue over the trajectory of treatment. Further research is needed into the biologic mechanisms of fatigue.

Introduction

Children and adolescents with cancer report that fatigue is a near-universal experience and one of the most distressing, treatment related symptoms; it interferes with normal developmental experiences and compromises overall quality of life (Hockenberry-Eaton and Hinds, 2000; Davies et al., 2002; Gibson et al., 2005; Erickson et al., 2010; Dupois et al., 2010). As we increase our understanding of fatigue in children and adolescents with cancer, it is important to explore new biologic measurements related to this symptom. Carnitine, a micronutrient derived from an amino acid, is found in nearly all cells of the body and plays a critical role in energy production (Foster, 2004). The possible association of carnitine deficiency and fatigue found in adult cancer patients (Cruciani et al., 2006), may provide an additional physiologic indicator for evaluation of fatigue in children and adolescents.

Fatty acids are a primary source of energy for humans, especially in the cardiac and skeletal systems (National Institutes of Health, 2013). The micronutrient, carnitine, transports long-chain fatty acids across the membranes of the muscle cell's mitochondria. Using β-oxidation, the fatty acids are metabolized into energy (adenosine triphosphate [ATP]). Additionally, carnitine also transports fatty acids back out of the mitochondria that accumulate as a result of normal and abnormal metabolism (Foster, 2004). Carnitine

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plasma levels are further regulated through the proximal tubules of the kidney where it is reabsorbed through a specific transport system (Foster, 2004). Because skeletal and cardiac muscles use fatty acids as their primary source of energy, deficiencies in carnitine are manifested as low energy levels and muscular weakness (Cruciani et al., 2004).

Cancer researchers have identified how chemotherapy drugs interfere with the carnitine network (Peluso et al., 2000) and this research has primarily focused on three agents: doxorubicin, ifosfamide, and cisplatin. Doxorubicin hinders the carnitine system by reducing heart concentrations of free carnitine, decreasing free fatty acid oxidation, creatine phosphate, and protein synthesis and oxygen uptake (Peluso et al., 2000; Waldner et al., 2006) The metabolic pathways of ifosfamide, leads to formation of chloroacetyl-CoA with a decrease in CoASH levels, an activator of energy-providing systems. Carnitine binds to the chloroacetyl-CoA, detoxifies it, and the chloro-acteyl-carnitine is excreted in the urine. This detoxification results in a secondary deficiency of carnitine in patients receiving ifosfamide (Peluso et al., 2000; Sayed-Ahmed et al., 2012). Cisplatin can damage the kidney resulting in a reduction in glomerular filtration and tubular damage. Carnitine is absorbed in the body proximal to the tubular level and patients receiving cisplatin can have an increased loss of carnitine through the kidney (Peluso et al., 2000).

Carnitine is measured in blood plasma using tandem mass spectrometry (MS/MS) stable isotope dilution analysis. Free carnitine (FC) is a measure of the L-carnitine available for transporting fatty acids into the mitochondria. Total carnitine (TC) is the L-carnitine plus acyl-carnitine (AC); AC is the waste product after the body has used the L-carnitine. Carnitine deficiency is defined biochemically as abnormally low plasma levels of FC. Carnitine level results also include the ratio of AC (TC minus FC) to FC and it is reported as the AC/FC ratio (Schmidt-Sommerfeld, Werner, & Penn, as cited in Mayo Medical Laboratories, 2014). Pediatric reference values for carnitine plasma levels can be seen in Table 1.

In children with cancer, researchers have measured changes in carnitine levels during chemotherapy treatment. In a cohort of children ($n = 51$) aged 3–16 years with a variety of oncologic diagnoses and treatments, serum carnitine levels were similar to healthy controls at diagnosis. After three months of treatment, the children with cancer had a significant decrease in carnitine levels and these measurements were significantly different than the healthy controls (Yaris et al., 2002). Rogalidou et al. (2010) studied 40 children and adolescents with acute leukemia over the trajectory of treatment and survivorship, measuring carnitine levels at diagnosis, after 1 year of treatment, at the end of treatment and 2 years after treatment. There was a significant, transient decrease in total and free carnitine during the first year of treatment with levels recovering after treatment. Khositseth et al. (2011) recently studied carnitine levels in a small group of children ($n = 9$) with solid tumors who were treated with doxorucibin. Carnitine measurements occurred after cumulative dose of doxorubicin $\geq$150 and 300 mg/m^2, respectively. Carnitine levels did not change significantly from baseline.

Table 1
Carnitine reference values (ranges).

Age group	Total*	Free*	Acylcarnitine*	AC/FC ratio
3–6 years	35–84	24–63	4–28	0.1–0.8
7–10 years	28–83	22–66	3–32	0.1–0.9
11–17 years	34–77	22–65	4–29	0.1–0.9
18 years or older	34–78	24–54	5–30	0.1–0.8

* Values expressed as μmol/L (Schmidt-Sommerfeld, Werner, & Penn, as cited in Mayo Medical Laboratories, 2014).

In our program of fatigue research, we have completed two studies examining the influence of carnitine on fatigue levels. In a study of 67 pediatric cancer patients receiving ifosfamide, cisplatin, or doxorubicin chemotherapy, fatigue and carnitine plasma levels were measured day 1 before chemotherapy started and 7 days after chemotherapy was initiated. Overall, there was a significant increase in free and total carnitine levels after treatment for patients receiving doxorubicin (Hockenberry et al., 2009). This finding supported the observation of others (Heuberger et al., 1998) that carnitine may be released by tissues into the bloodstream to replace carnitine loss through renal excretion resulting in the initial increase in plasma levels. For the subset of children and adolescents who had received prior chemotherapy, increased fatigue and decreased carnitine were significantly correlated a week after chemotherapy (Hockenberry et al., 2009). In the next study, fatigue and carnitine were measured in 30 children between days 15 and 29 during the 1st and 3rd cycles of chemotherapy. In school-age children, carnitine levels decreased significantly but so did fatigue levels, while in adolescents both carnitine levels and fatigue remained unchanged (Hooke, 2009). Carnitine levels for all participants remained within the pediatric reference range. As with the first study, there were no significant changes in AC levels or in the AC/FC ratio. Our studies support that carnitine may increase initially but then decrease over time.

In this study, we sought to measure carnitine plasma levels beyond the third cycle of treatment in order to gain further insight into the trajectory of carnitine plasma levels and their relationship to fatigue. The study aims were:

1. To examine the change in carnitine plasma levels in childhood cancer patients receiving ifosfamide, cisplatin, or doxorubicin over multiple cycles of chemotherapy treatment.
2. To examine the change in levels of fatigue in childhood cancer patients receiving ifosfamide, cisplatin, or doxorubicin over multiple cycles of chemotherapy treatment.
3. To examine the influence of carnitine plasma levels on fatigue in children and during this treatment period.

Conceptual framework

The organizing framework for the study was an adaptation of the **Symptoms Experience Model** (SEM) (Armstrong, 2003; Dodd et al., 2001). The adapted SEM identifies person, environmental, and disease factors as antecedents that influence the individual's symptom experiences during treatment for cancer. In this model, person factors include gender and developmental age. Environmental factors include frequent hospitalizations for chemotherapy. Disease factors influencing the symptom experiences in children with cancer include the type of cancer and type of chemotherapy administered. The specific chemotherapy drugs, (doxorubicin, ifosfamide, cisplatin) require carnitine to be metabolized in the body which may create a deficit. Carnitine is required for fatty acid oxidation in the muscles and a carnitine deficit can contribute to muscle weakness and a sensation of physical fatigue. In this study, we hypothesized that carnitine deficiency would occur over the trajectory of treatment and would contribute to the intensity of the symptom of fatigue.

Methods

A repeated-measures research design was used to evaluate whether children and adolescents receiving cisplatin, ifosfamide and/or doxorubicin experienced a carnitine deficiency and increased fatigue. Children and adolescents were followed starting with the 2nd cycle of chemotherapy for multiple cycles.