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Safety, tolerability and symptom outcomes associated with L-carnitine supplementation in patients with cancer, fatigue, and carnitine deficiency: a phase I/II study.

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Abstract

Carnitine deficiency is among the many metabolic disturbances that may contribute to fatigue in patients with cancer. Administration of exogenous L-carnitine may hold promise as a treatment for this common symptom. Little is known about L-carnitine safety, tolerability, and dose-response in patients with cancer. We conducted a Phase I/II open-label trial to assess the safety and tolerability of exogenous L-carnitine and clarify the safe dose range associated with symptom effects for future controlled trials. Adult patients with advanced cancer, carnitine deficiency (free carnitine <35 for males or <25 microM/L for females, or acyl/free carnitine ratio >0.4), moderate to severe fatigue, and a Karnofsky Performance Status (KPS) score > or =50 were entered by groups of at least three into a standard maximum tolerated dose design. Each successive group received a higher dose of L-carnitine (250, 750, 1250, 1750, 2250, 2750, 3000 mg/day, respectively), administered in two daily doses for 7 days. To compare symptom outcomes before and after supplementation, patients completed validated measures of fatigue (Brief Fatigue Inventory [BFI]), depressed mood (Center for Epidemiologic Studies Depression Scale [CES-D]), quality of sleep (Epworth Sleeplessness Scale [ESS]), and KPS at baseline and 1 week later. Of the 38 patients screened for carnitine levels, 29 were deficient (76%). Twenty-seven patients participated ("intention to treat, ITT") (17 males, 10 females), and 21 completed the study ("completers"); 17 of these patients ("responders," mean+/-[SD] age=57.9+/-15) had increased carnitine levels at the end of the supplementation period. The highest dose achieved was 3000 mg/day. No patient experienced significant side effects and no toxicities were noted. Analysis of all the patients accrued (ITT, n=27) showed a total carnitine increase from 32.8+/-10 to 54.3+/-23 microM/L (P<0.001) and free carnitine increase from 26.8+/-8 to 44.1+/-17 microM/L (P<0.001). BFI decreased significantly, from 66+/-12 to 39.7+/-26 (P<0.001); ESS decreased from 12.9+/-12 to 9+/-6 (P=0.001); and CES-D decreased from 29.2+/-12 to 19+/-12 (P<0.001). A separate analysis of the 17 "responders" showed a dose-response relationship for total- (r=0.54, P=0.03), free-carnitine (r=0.56, P=0.02) levels, and fatigue (BFI) scores (r=-0.61, P=0.01). These findings suggest that l-carnitine may be safely administered at doses up to 3000 mg/day and that positive effects may be more likely at relatively higher doses in this range. This study provides the basis for the design of future placebo-controlled studies of l-carnitine supplementation for cancer-related fatigue.

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