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ORIGINAL ARTICLE

Urinary excretion of L-carnitine and its short-chain acetyl-L-carnitine in patients undergoing carboplatin treatment

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Abstract
Purpose To evaluate the effect of the anti-cancer drug carboplatin on plasma concentrations and urinary excretion of L-carnitine (LC) and its main ester, acetyl-L-carnitine (ALC), in cancer patients.
Methods Plasma and urine concentrations of LC and ALC from 11 patients on carboplatin therapy (1 h intravenous infusion; AUC dose 4.8 ± 1.1 mg/ml min) in combination with docetaxel, paclitaxel or vinorelbine, were determined by high-performance liquid chromatography with fluorimetric detection.
Results Before carboplatin therapy, the mean ± SD plasma concentrations of LC and ALC were 47.8 ± 10.9 and 7.04 ± 1.04 nmoles/ml, respectively, and remained constant throughout the entire study period. In contrast, urinary excretion of LC and ALC, increased significantly during the chemotherapy from 115 ± 105 to 480 ± 348 μmoles/day ($P < 0.01$) and from 41 ± 41 to 89 ± 52 μmoles/day ($P < 0.05$) for LC and ALC, respectively, subsequently reverting to normal 6 days after the end of chemotherapy. Similarly, the renal clearance of LC and ALC increased substantially during chemotherapy from 1.67 ± 1.43 to 9.05 ± 9.52 ml/min ($P < 0.05$) and from 4.02 ± 4.51 to 7.97 ± 5.05 ml/min (P = not significant) for LC and ALC, respectively, reverting to normal 6 days after the end of chemotherapy. Plasma concentrations and urinary excretion of glucose, phosphate and urea nitrogen and creatinine clearance, however, were not affected by carboplatin therapy, indicating no impaired kidney function.
Conclusion Treatment with carboplatin was associated with a marked urinary loss of LC and ALC, most likely due to inhibition of carnitine reabsorption in the kidney.

Keywords L-Carnitine · Acetyl-L-carnitine · Carboplatin · Renal clearance · Urinary excretion

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Introduction

L-Carnitine (β-hydroxy-γ-trimethylaminobutyrate; LC) is an endogenous compound that plays an important physiological role in the transfer of long-chain fatty acids across the inner matrix membrane of mitochondria for their β-oxidation with energy production [2]. In humans, LC homeostasis is maintained by a modest biosynthesis within the body, absorption from dietary sources, and efficient renal tubular reabsorption from glomerular filtrate [25]. Since LC and its short-chain ester, acetyl-L-carnitine (ALC) are highly polar compounds, transport systems are involved to maintain concentration gradients between extracellular and intracellular LC (and ALC) in most tissues [25]. In the

kidney, the transport systems ensure that the body conserves LC, ALC and other acyl-L-carnitine derivatives (hereinafter, when used as a carnitine pool, these will be referred to ''carnitines''). Under homeostatic conditions more than 95% of the LC filtered load is reabsorbed by the renal tubule [8, 25].

The tubular reabsorption of LC, ALC and other acyl-L-carnitine derivatives could be impaired by many factors with a consequent increased loss of these compounds in the urine. Patients with primary carnitine deficiency show a genetic defect of the high-affinity carnitine transporter in many tissues. At renal level this results in an excessive loss of carnitines in the urine and leads to low-LC concentrations in plasma [22]. Furthermore, subjects with metabolic diseases (renal tubular acidosis, fatty acid oxidation and branched-chain amino-acid disorders), particular nutritional states (fasting) and accelerated catabolism (hyperthyroidism, trauma, sepsis, burns and surgery) show an increased urinary excretion of LC and its acyl ester derivatives [9, 14, 21]. Finally, the administration of several drugs (valproic acid, pivalic acid-containing prodrugs and cephalosporins) is capable of altering the urinary profile of LC, thereby decreasing its reabsorption in the kidney, probably related to a transporter-mediated interaction between LC and the drug administered [10, 20].

Recently, in patients treated with the antineoplastic agent cisplatin, the urinary excretion of LC (and acyl-L-carnitine derivatives) increased dramatically [13]. This high renal wasting persisted over the 3 days of cisplatin treatment and was reversed only 7 days after discontinuing the treatment. In addition, cisplatin treatment does not affect physiological parameters such as glomerular filtration rate, or glucose and phosphate reabsorption, indicating no renal damage. Consequently, it was suggested that cisplatin could increase the excretion of LC (and acyl-L-carnitine derivatives) by inhibiting their transport system [13].

Carboplatin, a second-generation platinum-containing anti-cancer drug, is currently used against lung, ovarian, head and neck cancers [3, 30]. The compound is extensively cleared unmodified by the kidney with a renal clearance related to the glomerular filtration rate [30]. Although the compound shows a lack of nephrotoxicity at conventional doses, the predominantly urinary excretion of carboplatin could affect the reabsorption of LC and ALC, as demonstrated for its analogue cisplatin. The present study was conducted to evaluate the effect of carboplatin treatment on plasma concentrations and urinary excretion of LC and ALC in cancer patients.

Patients and methods

Study design

The study involved 11 patients (six females and five males), aged 47–79 years, body mass index (BMI) 21.5–32.4 kg/m^2, undergoing carboplatin therapy at a general hospital oncology centre. The protocol was approved by the institutional board of the hospital and all the patients gave written informed consent. The study consisted of four-time periods, each of 24 h: a baseline period (day –1), a treatment period (day 0), and days 1 (day +1) and 6 (day +6) after treatment. During day 0, carboplatin was administered by intravenous infusion for 1 h. Concomitant chemotherapy, consisting of docetaxel, paclitaxel and vinorelbine was administered immediately before the carboplatin therapy.

Sampling

During each period, patients were instructed to empty their bladders before starting the urine collection. The urine was collected in a plastic container with previous addition of hydrochloric acid (1.0 M; 5 ml/l) and kept in a refrigerator until the end of collection. Furthermore, excluding day 0, patients were asked to collect their urine at home, taking particular care with the collection. The urine container was then delivered to the hospital oncology centre and urine volume was recorded. Four aliquots (5 ml) of each sample were stored (–20°C) for later analysis.

Blood samples for clinical and pharmacokinetic analysis were obtained from the side contralateral to drug administration at the following times: at the end of baseline urine collection (day –1), after the end of carboplatin therapy (day 0), and at the end of the subsequent urine collections (days +1 and +6), respectively. This schedule was to avoid the patients having to return several times to the hospital centre for blood drawing.

Blood samples (5 ml) were taken by venepuncture, placed in a heparinized Vacutainer (Beckton-Dickinson, Rome, Italy) and immediately centrifuged (2,000*g*, 10 min), to obtain plasma (2–3 ml). Four aliquots (0.5–1.0 ml) of each sample were stored at –20°C until analysed.

Assay method

Plasma concentrations of LC and ALC were determined by high-performance liquid chromatography (HPLC), as described previously [16].

The concentration of LC and ALC in urine could not be assayed by this method because of unresolved

peaks arising from endogenous compounds. Therefore, a validated HPLC method in urine was used (Sigma-Tau, Pomezia, Italy, internal report). Briefly, LC and ALC were separated on a 5 μm, 250 × 4.6 mm Zorbax SCX column (Agilent, Rome, Italy) and quantified by means of fluorimetric detection [16]. The mobile phase consisted of tris-(hydroxymethyl)aminomethane buffer (450 mmoles/l), pH 5, containing methanol (75%) and acetonitrile (15%). The flow rate was set at 0.8–1 ml/min, and the eluents were monitored with an excitation wavelength of 248 and an emission wavelength of 418 nm. To measure LC and ALC, 0.1 ml of urine was diluted with 0.35 ml of phosphate buffer (0.01 mol/l; pH 7.0), 0.05 ml of an aqueous solution of internal standard and processed as for the plasma [16]. Together with the unknown samples, urine calibration curves for LC (10–80 nmoles/ml) and ALC (2–16 nmoles/ml) were also measured. For the preparation of the calibration curves, bidistilled water was used as a matrix. The unknown concentrations of LC and ALC were calculated from the ratios of the peak areas of the analytes and internal standard by means of the corresponding calibration curves. The mean extraction recovery rates were 94 and 89% for LC and ALC, respectively. The accuracy and precision exceeded 80% with a coefficient of variation of less than 12%. Typical chromatograms of standards and urine extracts are shown in Fig. 1.

Plasma and urine concentrations of creatinine, glucose, phosphate and urea nitrogen were determined on a Cary 50 spectophotometer (Varian, Leinì, Turin, Italy) using commercial kits (Randox Laboratories, Crumlin, UK; Dade Behring, Milan, Italy) according to the manufacturers' instructions.

Calculations and statistics

The renal clearance of L-carnitine (CL_{LC}) or acetyl-L-carnitine (CL_{ALC}) was estimated as the rate of excretion in urine divided by plasma concentration:

$$CL = [(Urine)] \times UFR]/(Plasma),$$

where (Urine) and (Plasma) represent the concentrations of analyte in urine and plasma, respectively, and UFR is the urine flow rate (ml/min).

Creatinine clearance (CL_{CREAT}) was calculated using the following equation [5]:

$$CL_{CREAT} = (140 - Age) \times Weight \times (1 - 0.15 \times Sex)/72 \times (Plasma) \times 0.0113,$$

where weight is expressed in kilogram, and Sex is 1 if female or 0 if male; (Plasma) is the plasma creatinine concentration expressed in mg/dl.

Statistical comparisons were performed using analysis of variance (ANOVA) followed by post hoc analysis contrasts if significance was detected. $P < 0.05$ was considered significant. All data are presented as mean ± standard deviation (SD).

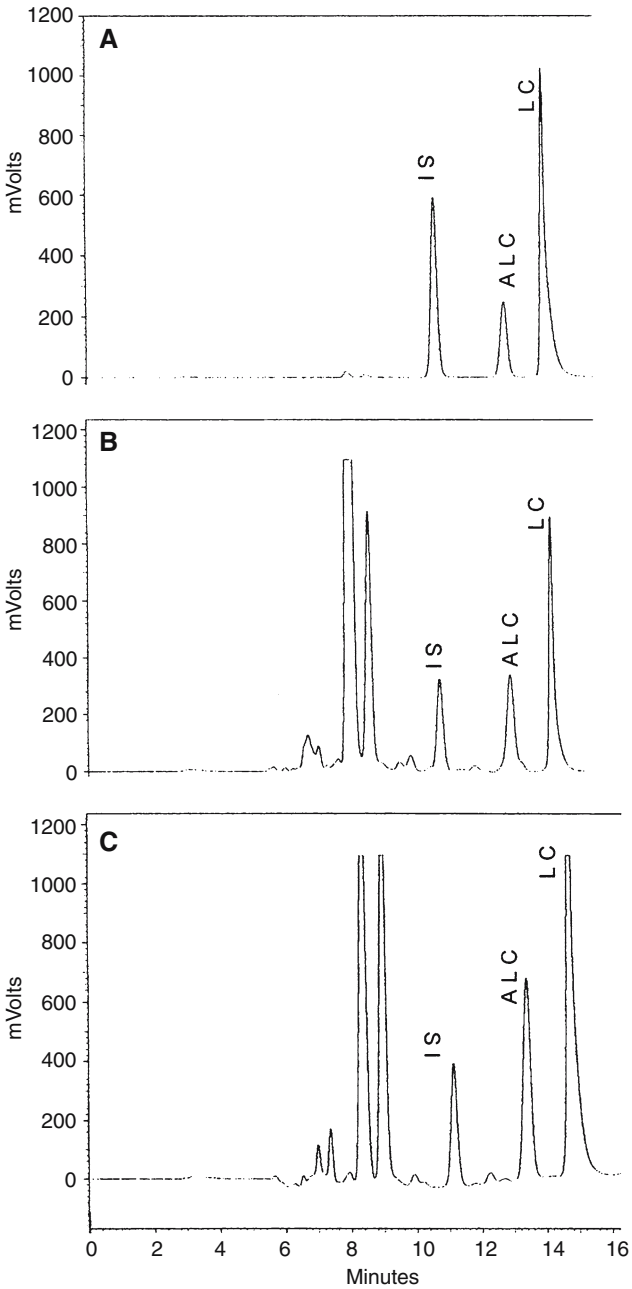

Fig. 1 Representative HPLC chromatogram of an LC (40 nmoles/ml), ALC (8 nmoles/ml) and Internal Standard (*IS*, 40 nmoles/ml) standard solution (**a**); urine sample from a tumour patient before (**b** day –1) and during (**c** day 0) carboplatin treatment

Results

Patient characteristics

Table 1 lists the characteristics of the 11 patients (five males and six females) recruited in this study. Patients were aged 47–79 with a fairly well-matched BMI (26.1 ± 3.9 kg/m^2), except for patients 3 and 10 (BMI: 32.4 and 32.5 kg/m^2, respectively). All patients received a carboplatin dose expressed as AUC (mg/ml min) from 4 to 6 with a mean (±SD) of 4.8 ± 1.1. The chemotherapy ranged from 1 to 7 cycles, respectively. Concomitant chemotherapy including the drugs paclitaxel, docetaxel and vinorelbine was administered to ten patients and was considered a common regimen for these patients' malignancies (Table 1).

Effect of carboplatin treatment on plasma concentration and urinary excretion of glucose, phosphate and nitrogen

Plasma concentrations of glucose, phosphate and urea nitrogen were found to lie within the normal ranges for healthy subjects (normal values as reported by diagnostic kits: glucose = 4.5–5.6 μmoles/ml; phosphate = 0.8–1.5 μmoles/ml; urea nitrogen = 3.75–17.8 μmoles/ml) and were not significantly affected by treatment with carboplatin (Fig. 1).

Urine excretion of glucose and phosphate, as well as urea nitrogen, resulted within the normal range of health subjects (normal values as reported by diagnostic kits: glucose = 4.5–5.6 mmoles/day; phosphate = 12–40 mmoles/ml; urea nitrogen = 250–715 mmoles/ml). None of the substrates were significantly affected by treatment with carboplatin (Fig. 1).

Effect of carboplatin treatment on plasma concentrations and urinary excretion of L-carnitine and acetyl-L-carnitine

Plasma concentrations of LC and ALC are shown in Fig. 2. Prior to carboplatin treatment (day –1) the plasma concentrations of LC and ALC were 47.8 ± 10.9 and 7.04 ± 1.04 nmoles/ml, respectively (Fig. 2). At days 0, +1 and +6, both the LC and ALC plasma concentrations remained almost constant compared with their pre-treatment values (Fig. 2).

Urinary excretion of LC and ALC is shown in Fig. 3. During administration of carboplatin (day 0) the urinary excretion of LC increased to 480 ± 348 μmoles/day and returned to the day –1 values (115 ± 105 μmoles/day) 6 days after discontinuing treatment (127 ± 152 μmoles/day). The amount of LC excreted on day 0 was significantly different ($P < 0.01$) from that recorded prior to carboplatin treatment. Furthermore, the increased excretion of LC remained high (322 ± 257 μmoles/day) after 1 day of treatment (day +1), though the difference was not statistically significant compared to pre-treatment values (Fig. 4).

Urinary excretion of ALC showed a similar trend to that of LC (Fig. 4). At day 0 the urinary excretion of ALC increased significantly ($P < 0.05$) to 89 ± 53 μmoles/day compared to pre-treatment values (41 ± 40 μmoles/day). Thereafter, the amount of ALC excreted remained fairly high until day +1 (72 ± 46 μmoles/day), though again the difference was not statistically significant compared to the day –1 values. At day +6, the urinary excretion of ALC decreased dramatically to values, which were half (19 ± 11 μmoles/day) those recorded prior to carboplatin treatment (Fig. 4).

Table 1 Patient characteristics

Patient number	Age (year)	Gender	Weight (kg)	BMI (kg/m^2)	Primary tumour site	Carboplatin AUC dose (mg/ml min)	Chemo-therapy cycle	Concomitant chemo-therapy
1	47	Female	55	21.5	Ovary	6.01	3	Docetaxel
2	79	Male	61	25.1	Bladder	2.03	1	–
3	60	Female	83	32.4	Breast	3.97	5	Vinorelbine
4	62	Male	66	26.4	Lung (nsclc)	4.89	7	Vinorelbine
5	76	Female	55	25.1	Ovary	4.52	1	Paclitaxel
6	69	Female	54	20.3	Ovary	5.00	6	Paclitaxel
7	49	Female	69	22.8	Ovary	5.61	5	Paclitaxel
8	59	Female	69	29.1	Ovary	5.03	6	Paclitaxel
9	72	Male	73	26.5	Lung (nsclc)	5.32	3	Vinorelbine
10	72	Male	73	25.2	Lung (nsclc)	6.06	2	Vinorelbine
11	79	Male	75	32.5	Lung (nsclc)	4.64	1	Vinorelbine

BMI Body mass index, *AUC* Area under the curve, *nsclc* Non-small cell lung cancer

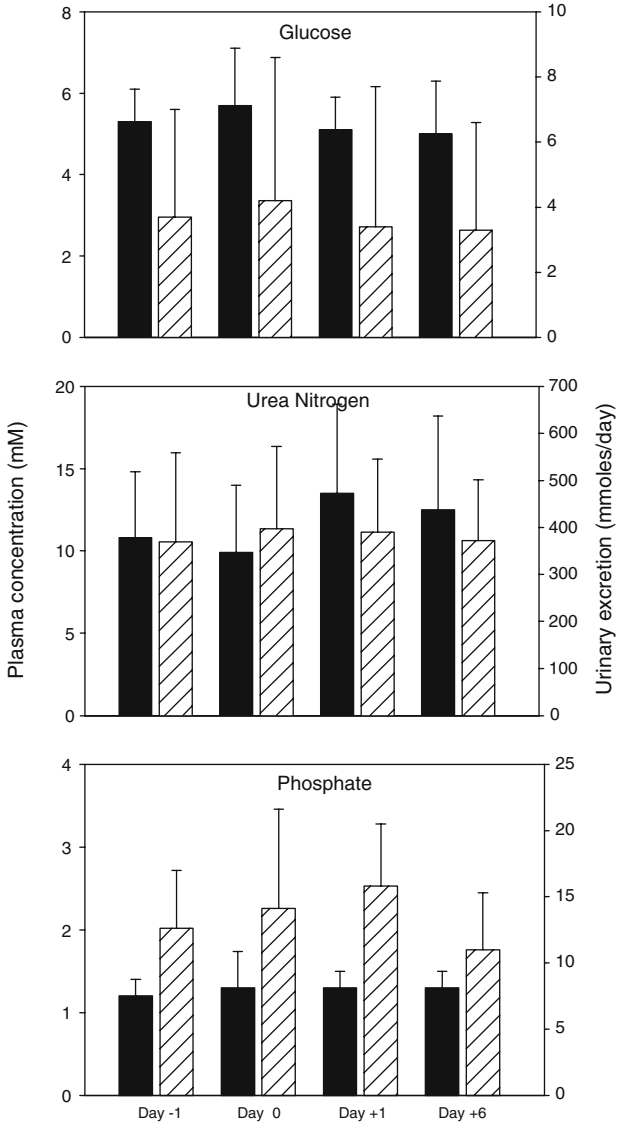

Fig. 2 Plasma concentration (*black bars*) and urinary excretion (*striped bars*) of glucose, urea nitrogen and phosphate in patients treated with carboplatin. The data presented are mean ± SD of 11 patients

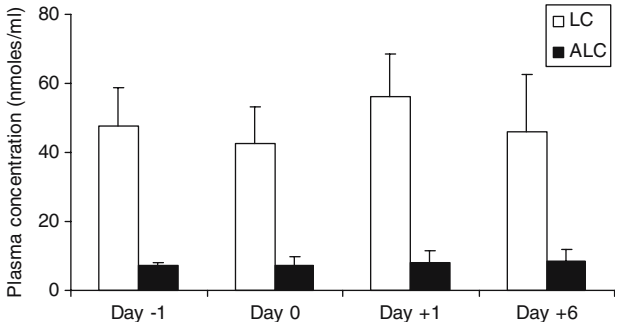

Fig. 3 L-Carnitine and acetyl-L-carnitine plasma concentrations (nmoles/ml) before (day –1), during (day 0) and after (days +1 and +6) carboplatin treatment. Each *bar* represents the mean ± SD of 11 patients

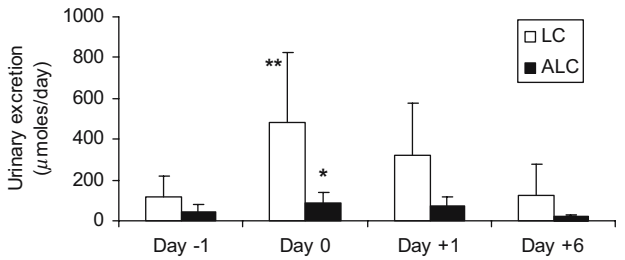

Fig. 4 L-Carnitine and acetyl-L-carnitine urinary excretion (μmoles/day) before (day –1), during (day 0) and after (days +1 and +6) carboplatin treatment. Each *bar* represents the mean ± SD of 11 patients (**$P < 0.01$, *$P < 0.05$, one-way ANOVA with post hoc analysis contrasts)

Effect of carboplatin treatment on the renal clearance of L-carnitine, acetyl-L-carnitine and creatinine

Renal handling of LC and ALC is shown in Table 2. At day –1, the CL_{LC} and CL_{ALC} values were 1.67 ± 1.43 and 4.02 ± 4.51 ml/min, respectively. Although the CL_{ALC} exceeded that of LC, the renal clearance values proved substantially lower for both compounds than the CL_{CREAT} values (72.89 ± 25.96 ml/min). During carboplatin treatment, CL_{LC} increased more than five times (9.05 ± 9.52 ml/min; $P < 0.05$ versus day –1) with a slow decrease at day +1 (3.99 ± 3.16 ml/min) and a return to the initial values at day +6 (1.35 ± 0.96 ml/min; Table 2).

As in the case of CL_{LC}, a similar trend towards a time-dependent increase in CL_{ALC} was evident during (day 0) and 1 day after carboplatin treatment (day +1) with a return to pre-treatment values 6 days after treatment (Table 2). However, the 49.6 and 39.4% increases in CL_{ALC} at days 0 and +1, respectively, failed to prove statistically significant (Table 2). In contrast to LC, CL_{CREAT} was not significantly affected by treatment with carboplatin and the values were almost constant throughout the entire period of the experiment. Considerable intraindividual variation was found, however, for all three clearances (LC, ALC and creatinine) (Table 2).

Discussion

It has been widely reported that the kidney is intimately involved in the homeostatic regulation of the carnitine pool [25]. Endogenous circulating LC, which is freely filtered at the glomerulus and extensively

Table 2 Renal clearance of L-carnitine, acetyl-L-carnitine and creatinine in patients treated with carboplatin

	L-carnitine	Acetyl-L-carnitine	Creatinine
Day –1	1.67 ± 1.43	4.02 ± 4.51	73 ± 26
Day 0	9.05 ± 9.52*	7.97 ± 5.05	74 ± 28
Day +1	3.99 ± 3.16	6.65 ± 4.38	65 ± 20
Day +6	1.35 ± 0.96	1.78 ± 1.06	69 ± 27

Values are mean ± SD of 11 patients. Units are ml/min

*Significantly different at $P < 0.05$ from day –1 group using ANOVA

reabsorbed at the proximal tubules, is eliminated from the body via renal excretion in the form of LC, ALC and other acylcarnitine esters [17, 19].

However, when genetic and/or metabolic diseases, particular conditions such as fasting, burns, or administration of drugs inhibiting its renal transport impair the tubular reabsorption of LC, a remarkable urinary loss of LC, ALC and acylcarnitines occurs [4, 9, 10, 20, 21, 23, 29]. In the present study, conducted in 11 cancer patients on carboplatin treatment, we observed an increased urinary excretion of endogenous LC and ALC, but no abnormal plasma concentrations (Figs. 3, 4).

In all the patients investigated, the mean plasma concentrations of LC and ALC before, during and after carboplatin treatment remained almost constant with values within the normal range for healthy subjects in whom 35–50 and 5–15 nmoles/ml for LC and ALC, respectively, have been reported [16]. This finding is in agreement with previous reports describing plasma concentrations of the above substrates in cancer patients [26, 33, 34]. However, alterations (decrease/increase) in the mean plasma LC concentrations of patients suffering from cancer have been observed in other studies [7, 31]. The likely explanation could be due to the heterogeneity of cancer patients in these studies (e.g. age, sex, tumour type and stage, chemotherapy and nutritional state). Patients reporting moderate to severe fatigue, or exhibiting a cachectic state present lower than normal LC plasma concentrations [6, 11, 31].

As regards the daily urinary excretion of LC and ALC before carboplatin treatment, our cancer patients had values (Fig. 4) similar to those encountered in healthy subjects [7, 18].

Furthermore, no impaired kidney function, as shown by normal values of CL_{CREAT} or plasma and urinary excretion of glucose, urea nitrogen and phosphate was found in these patients (Table 2; Fig. 2). Thus, the good kidney function in these patients, together with the constant plasma concentrations of circulating LC and ALC, resulted in renal clearances of 4.02 ± 4.51 and 1.67 ± 1.43 ml/min for LC and ALC, respectively.

These values are similar to those encountered in healthy subjects [19], suggesting no alteration of renal handling of LC and ALC in cancer patients. In addition, for both LC and ALC, whose binding to plasma proteins is negligible, the renal clearance was substantially less than the glomerular filtration rate, expressed as CL_{CREAT}, indicating extensive renal reabsorption in these patients (Table 2). Although the report by Dodson et al. [7] shows an elevated urinary excretion of LC and ALC in cancer patients compared with healthy controls, the renal handling of these substrates was compatible with their remarkable reabsorption in the patients investigated, as observed in our study (Table 2).

It has been reported that a number of antineoplastic agents such as ifosfamide and carboplatin increase the urinary excretion of LC, ALC and other acylcarnitines [13, 18]. However, whereas, in the case of ifosfamide, cancer patients lose ~10% of their body carnitine store during one chemotherapy cycle, a more limited loss (5–7%) occurs during a cisplatin therapy cycle [13]. Our present results show that the wasting of LC and ALC from the body amounted to only 2% during one carboplatin therapy cycle.

In the present experiments, in which the patients received a carboplatin AUC dose within the range of 2.0–6.0 mg/ml min, generally considered non-nephrotoxic, changes in renal handling of LC and ALC were observed (Fig. 4; Table 2). During the treatment, the renal clearances of both LC and ALC increased by factors of 5.4 and 1.98, respectively, and remained so 1 day after the end of the treatment (Table 2). Interestingly, the ratio of CL_{LC} (or CL_{ALC}) to glomerular filtration rate was less than unity, indicating that LC (or ALC) continues to be eliminated in urine by a tubular reabsorption mechanism also during carboplatin treatment. Thus, carboplatin, which is extensively cleared unmodified by the kidney, could compete at the level of tubular reabsorption of LC and ALC, through interaction with LC (or ALC) specific transporters, leading to less reabsorption of these substrates, as reflected by their increased elimination in urine (Fig. 3).

In light of present results, it is possible that the increased urinary loss LC and ALC can result in significant reduction of these compounds in the body,

particularly after numerous carboplatin chemotherapy cycles. Considering the central role of LC in energy metabolism of mammalian cells [2], a possible carnitine deficiency could contribute to the development of chemotherapy-induced fatigue [6, 11, 31].

A large number of studies have reported that a family of organic transporters designated organic/carnitine transporters (Octn) are responsible for LC transport in cell membranes [15]. The most important carnitine transporter is Octn2, which is capable of transporting LC as well as ALC and other acylcarnitines. In general, Octn2 is most expressed in the kidney, where it is mainly involved in carnitine reabsorption [28]. Although LC reabsorption via Octn2 may be inhibited by LC analogues, other drugs structurally unrelated to LC are recognized by Octn2 and enabled to impair the reabsorption of LC [24, 28, 32]. Thus, we suggest that carboplatin may be a good inhibitor of Octn2-mediated carnitine transport, though other mechanisms cannot be excluded. Thus, further investigations, at cellular and molecular level will be necessary to characterize the site(s) and mechanism(s) of inhibition of LC (and ALC) renal reabsorption.

Finally, it could be argued that the increased urinary loss of LC and ALC during carboplatin treatment may be caused by the concomitant administration of anticancer drugs in these patients (Table 1). Considering the pharmacokinetic behaviour of taxanes (docetaxel, paclitaxel) and vinorelbine, these drugs appear to undergo predominantly hepatic elimination (more than 90% excretion in the faeces as parent drug and metabolites), while the kidney plays only a negligible role in their disposition [1, 12, 27].

Therefore, the above-mentioned hypothesis could be easily refuted.

In conclusion, the results of this study show that treatment with carboplatin was associated with a marked urinary loss of LC and ALC, which was due not to any nephrotoxic action of the compound but most probably to inhibition of carnitine reabsorption in the kidney.

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References

1. Baker SD, Sparreboom A, Verweij J (2006) Clinical pharmacokinetics of docetaxel: recent developments. Clin Pharmacokinet 45:235–252
2. Bieber LL (1988) Carnitine. Annu Rev Biochem 57:261–283
3. Boulikas T, Vougiouka M (2004) Recent clinical trials using cisplatin, carboplatin and their combination chemotherapy drugs (review). Oncol Rep 11:559–595
4. Bowyer BA, Fleming CR, Haymond MW, Miles JM (1989) L-carnitine: effect of intravenous administration on fuel homeostasis in normal subjects and home-parenteral-nutrition patients with low plasma carnitine concentrations. Am J Clin Nutr 49:618–623
5. Cockcroft D, Gault M (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16:31–41
6. Cruciani RA, Dvorkin E, Homel P, Culliney B, Malamud S, Shaiova L, Fleishman S, Lapin J, Klein E, Lesage P, Portenoy R, Esteban-Cruciani N (2004) L-carnitine supplementation for the treatment of fatigue and depressed mood in cancer patients with carnitine deficiency. Ann N Y Acad Sci 1033:168–176
7. Dodson WL, Sachan DS, Krauss S, Hanna W (1989) Alterations of serum and urinary carnitine profiles in cancer patients: hypothesis of possible significance. J Am Coll Nutr 8:133–142
8. Engel AG, Rebouche CJ, Wilson DM, Glascow AM, Romshe CA, Cruse RP (1981) Primary systemic carnitine deficiency. II. Renal handling of carnitine. Neurology 31:819–825
9. Frohlich J, Seccombe DW, Hahn P, Dodek P, Hynie I (1978) Effect of fasting on free and esterified carnitine levels in human serum and urine: correlation with serum levels of free fatty acids and β-hydroxybutyrate. Metabolism 27:555–561
10. Ganapathy ME, Huang W, Rajan P, Carter AL, Sugawara M, Iseki K, Leibach FH, Ganapathy V (2000) β-Lactam antibiotics as substrates for OCTN2, an organic cation/carnitine transporter. J Biol Chem 275:1699–1707
11. Graziano F, Bisonni R, Catalano V, Silva R, Rovinati S, Mencarini E, Ferraro B, Canestrai F, Balzelli AM, De Gaetano A, Giordani P, Testa E, Lai V (2002) Potential role of levocarnitine supplementation for the treatment of chemotherapy-induced fatigue in non-anemic cancer patients. Br J Cancer 86:1854–1857
12. Gregory RK, Smith IE (2000) Vinorelbine: a clinical review. Br J Cancer 82:1907–1913
13. Heuberger W, Berardi S, Jacky E, Pey P, Krahenbuhl S (1998) Increased urinary excretion of carnitine in patients treated with cisplatin. Eur J Clin Pharmacol 54:503–508
14. Hoppel CL, Genuth SM (1980) Carnitine metabolism in normal-weight and obese human subjects during fasting. Am J Physiol Endocrinol Metab 238:E409–E415
15. Koepsell H (2004) Polyspecific organic cation transporters: their functions and interactions with drugs. Trends Pharmacol Sci 25:375–381
16. Longo A, Bruno G, Curti S, Mancinelli A, Miotto G (1996) Determination of L-carnitine, acetyl-L-carnitine and propionyl-L-carnitine in human plasma by high-performance liquid chromatography after pre-column derivatization with 1-aminoanthracene. J Chromatogr 686:129–139
17. Mancinelli A, Longo A, Shanahan K, Evans AM (1995) Disposition of L-carnitine and acetyl-L-carnitine in the isolated perfused rat kidney. J Pharmacol Exp Ther 274:1122–1128
18. Marthaler NP, Visarius T, Kupfer A, Lauterburg BH (1999) Increased urinary losses of carnitine during ifosfamide chemotherapy. Cancer Chemother Pharmacol 44:170–172
19. Marzo A, Arrigoni-Martelli E, Urso R, Rocchetti M, Rizza V, Kelly JG (1989) Metabolism and disposition of intravenously administered acetyl-L-carnitine in healthy volunteers. Eur J Clin Pharmacol 37:59–63
20. Melegh B, Kerner J, Bieber LL (1987) Pivampicillin-promoted excretion of pivaloylcarnitine in humans. Biochem Pharmacol 36:3405–3409

21. Natali A, Santoro D, Brandi LS, Faraffiana D, Ciociaro D, Pecori N, Buzzigoli G, Ferrannini E (1993) Effects of acute hypercarnitinemia during increased fatty substrate oxidation in man. Metabolism 42:594–600
22. Nezu J, Tamai I, Oku A, Ohashi R, Yabuuchi H, Hashimoto N, Nikaido H, Sai Y, Koizumi A, Shoji Y, Takada G, Matsuishi T, Yoshino M, Kato H, Ohura T, Tsujimoto G, Hayakawa J, Shimane M, Tsuji A (1999) Primary systemic carnitine deficiency is caused by mutation in a gene encoding sodium ion-dependent carnitine transporter. Nat Genet 21:91–94
23. Noble S, Goa KL (1999) Adefovir dipivoxil. Drugs 58:479–487
24. Ohashi R, Tamai I, Yabuuchi H, Nezu JI, Oku A, Sai Y, Shimane M, Tsuji A (1999) Na^+-dependent carnitine transport by organic cation transporter (OCTN2): its pharmacological and toxicological relevance. J Pharmacol Exp Ther 291:778–784
25. Rebouche CJ, Seim H (1998) Carnitine metabolism and its regulation in microorganisms and mammals. Annu Rev Nutr 18:39–61
26. Rossle C, Pichard C, Roulet M, Bergstrom F, Furst P (1989) Muscle carnitine pools in cancer patients. Clin Nutr 8:341–346
27. Rowinsky EK (1997) The development and clinical utility of the taxane class of antimicrotubule chemotherapy agents. Annu Rev Med 48:353–374
28. Tamai I, Ohashi R, Nezu J, Yabuuchi H, Oku A, Shimane M, Sai Y, Tsuji A (1998) Molecular and functional identification of sodium ion-dependent, high affinity human carnitine transporter OCTN2. J Biol Chem 273:20378–20382
29. Tune BM, Hsu CY (1994) Toxicity of cephaloridine to carnitine transport and fatty acid metabolism in rabbit renal cortical mitochondria: structure-activity relationships. J Pharmacol Exp Ther 270:873–880
30. Van der Vijgh WJF (1991) Clinical pharmacokinetics of carboplatin. Clin Pharmacokinet 21:242–261
31. Vinci E, Rampello E, Zanoli L, Oreste G, Pistone G, Malaguerra M (2005) Serum carnitine levels in patients with tumoral cachexia. Eur J Int Med 16:419–442
32. Wagner CA, Lukewille YU, Kaltenbach S, Moschen I, Broer A, Risler T, Broer S, Lang F (2000) Functional and pharmacological characterization of human Na^+-carnitine cotransporter hOCTN2. Am J Physiol Renal Physiol 279:F584–F591
33. Yaris N, Akyuz C (2002) Serum carnitine levels of pediatric patients. Pediatr Hematol Oncol 19:1–8
34. Yaris N, Ceviz N, Coskun T, Akyuz C, Buyukpamukcu M (2002) Serum carnitine levels during the doxorubicin therapy. Its role in cardiotoxicity. J Exp Clin Cancer Res 21:165–170