Nephrol Dial Transplant (1999) 14: 2819–2821

Saving erythropoietin by administering L-carnitine?

Jürgen Bommer

Universitätsklinik Heidelberg, Nephrology Department, Heidelberg, Germany

Introduction

Recombinant human erythropoietin (rhEpo) is widely used for correction of anaemia in patients with end-stage renal disease (ESRD). In some countries, the cost of rhEpo treatment accounts for up to 10% of total costs for chronic haemodialysis treatment. There is, therefore, a strong incentive to reduce the rhEpo requirement in dialysis patients by ancillary measures. Strategies with proven efficacy to reduce rhEpo requirement include: iron supplementation, subcutaneous mode of administration (compared with i.v. administration), correction of hyperparathyroidism, treatment of infections and correction of aluminium intoxication.

Several less well-proven procedures have recently been summarized by Hörl [1] among them the administration of L-carnitine. Against the above background it appears appropriate to discuss the evidence which argues for this suggestion [1].

Is L-carnitine deficiency found in patients on maintenance haemodialysis?

Whether L-carnitine deficiency exists in dialysis patients has not been established beyond doubt. In patients with preterminal renal failure, some authors have reported that serum concentrations of both free and total carnitine were increased, while the ratio of free carnitine to acylcarnitine was decreased in uraemic patients compared with controls [2–4]. The small water-soluble carnitine molecule is dialysable and a 75% decrease in plasma concentration has been noted during dialysis sessions [5]. Several hours after dialysis, however, L-carnitine concentrations return to predialytic values as a consequence of re-equilibration, i.e. the return of L-carnitine from tissue stores to the extracellular space. According to some authors, in patients who have been dialysed for many years, the post-dialytic rebound of free L-carnitine serum concentration is attenuated, and even a gradual decrease of predialytic free or total L-carnitine is observed [6].

Reduced predialytic serum concentrations of free L-carnitine, compared with healthy controls, have been found by some authors [3,7,8]. In contrast, normal or even elevated plasma concentrations of total carnitine have been reported by several authors [2,3,6]. The high total serum concentration of carnitine results predominantly from an increase in L-carnitine esters, i.e. acylcarnitine. As a result of the reduction in free carnitine, the ratios of free/total carnitine and free carnitine/acylcarnitine are decreased in dialysis patients [9]. It has been suggested that a decreased ratio of free carnitine to acylcarnitine resp. free carnitine to total carnitine indicates carnitine deficiency.

Plasma concentrations of L-carnitine and its subfractions may not be an adequate reflection of carnitine deficiency or carnitine availability in tissues and cells, i.e. the site where L-carnitine acts. Free carnitine concentrations in muscle have been reported to be subnormal in haemodialysis patients [10]. Savica *et al.* [11] reported a correlation between plasma free carnitine and muscle free carnitine.

In contrast to muscle, erythrocyte intracellular free carnitine concentrations are increased whereas the concentrations of acylcarnitine are comparable to normal controls; this results in an increased ratio of free to total carnitine [12].

The underlying mechanism of such changed plasma and cellular concentrations of carnitine and its subfractions has not been clarified. Intestinal absorption seems to be unchanged in dialysis patients [13]. There is limited information on the effect of L-carnitine supplementation on the plasma concentration of L-carnitine and its subfractions. Predialysis free plasma carnitine concentrations increased after oral L-carnitine. Unchanged free carnitine, but increased total carnitine plasma concentrations, have been found after i.v. carnitine substitution [12]. As a consequence, the ratio of free L-carnitine to total L-carnitine decreased [12].

Does L-carnitine affect increased erythrocyte fragility in uraemic patients?

By what mechanism could L-carnitine affect erythrocytes or erythroblasts? L-carnitine may influence erythrocyte stability and this would be consistent with a salutary effect of L-carnitine on erythrocyte survival. Alternative or complementary mechanisms of action of carnitine, e.g. on erythropoiesis, cannot be excluded, however, particularly since Trovato *et al.* [14] reported that L-carnitine increased reticulocyte counts. In dialysis patients erythrocyte survival is reduced markedly by ~50% [4,15]. Experimental studies and some clin-

Correspondence and offprint requests to: Jürgen Bommer, Department of Internal Medicine, Division of Nephrology, Bergheimer Str. 56. D-69115 Heidelberg, Germany.

ical observations suggest that L-carnitine increases erythrocyte survival. L-carnitine affects several erythrocyte characteristics which determine erythrocyte viability, e.g. osmotic resistance, stability under shear stress, Na^+-K^+-ATPase, etc. In the study by Bayon *et al.* [16] *in vivo* administration of carnitine increased the osmotic resistance of rat erythrocytes. This observation is of interest since Matsumura *et al.* [9] found a reduced osmotic stability of erythrocytes, determined by using a coil planet centrifuge method, and low plasma L-carnitine concentrations in 26 chronic haemodialysis patients. In this study a direct correlation was noted between the haemolysis endpoint and the plasma concentration of total carnitine and acylcarnitine. Furthermore, a significant correlation was found between the haemolysis maximum point and the plasma concentration of total and free carnitine.

Arduini *et al.* [17] noted that impaired mechanical stability of erythrocytes was improved by L-carnitine, while erythrocyte deformability remained unaffected. It has been postulated that L-carnitine stabilizes the erythrocyte membrane by improving the uptake of the lipids which form the plasma membrane. Radiolabelled carbon of acetylcarnitine was shown to accumulate in the phospholipid and triglyceride fractions, the major components of the erythrocyte membrane [18,19]. It is not only the composition and mechanical properties of erythrocytes that may be influenced. Carnitine may also affect functional properties of the erythrocyte membrane e.g. the activity of the Na^+-K^+-pump of the erythrocyte membrane. The activity of the Na^+-K^+-pump is instrumental in the maintenance of the biconcave discoid shape of erythrocytes. The activity of Na^+-K^+-ATPase of erythrocytes is inhibited by the addition of uraemic plasma [20,21], which reduces the number of pump sites, particularly in young erythrocytes. Labonia *et al.* [22] noted an increase of Na^+-K^+-pump activity of the erythrocyte membrane in uraemic patients after supplementation of L-carnitine. Carnitine increased ouabain-sensitive sodium efflux without changing the ouabain-insensitive sodium–potassium cotransport or sodium–lithium cotransport. The authors concluded that carnitine deficiency may play a role in the well-known dysfunction of Na^+-K^+-pump activity in uraemic patients. An elegant mechanistic explanation has been provided by Donatelli *et al.* [19]. Circulating free fatty acids are endogenous inhibitors of the Na^+-K^+-ATPase. L-Carnitine increases delivery of free fatty acid to the mitochondria for oxidation and as a result the plasma concentration of free fatty acids decreases and the inhibition of the Na^+-K^+-ATPase is reversed. The longer lifespan of rat blood cells after treatment with L-carnitine would be in agreement with this idea.

Does administration of L-carnitine improve anaemia?

Many years ago in an uncontrolled study, Albertazzi *et al.* [23] reported that the haematocrit increased from $23.1 \pm 5.32\%$ to $26.5 \pm 4.36\%$ after administration of 1 g/day carnitine per os for 6 months in 12 haemodialysis patients. Similar results were found in a second study of 11 haemodialysis patients who were dialysed with a dialysate containing 100 μmol/l L-carnitine. These results were subsequently confirmed in double-blind, placebo-controlled studies by Bellinghieri *et al.* [10]. A persistent long-lasting effect of carnitine administration was also noted in a placebo-controlled study by Trovato *et al.* [14]; a continuous increase in haematocrit was noted from $25.5 \pm 1.43\%$ to $37.4 \pm 2.2\%$ during 12 months of administration of L-carnitine. During the same interval haematocrit decreased in the placebo-controlled group from $24.0 \pm 3.58\%$ to $21.8 \pm 3.15\%$. The increase in haematocrit was paralleled by a progressive increase in absolute reticulocyte count by 40–60% in the carnitine, but not in the placebo group. Artefactual changes of iron status are excluded by the observation that the serum ferritin and transferrin levels remained constant and comparable in both groups throughout the entire study period. All patients received 10 mg sodium ferrigluconate intravenously at the end of the dialysis sessions. These observations in non-rhEpo-treated patients suggested that carnitine therapy might also permit more efficient use of rhEpo. A beneficial effect of L-carnitine on haemoglobin during rhEpo therapy in haemodialysis patients has been noted by several authors, e.g. Kooistra *et al.* [24], Boran *et al.* [25], Patrikarea *et al.* [26] and Kavadias *et al.* [27]. In a prospective placebo-controlled study Labonia *et al.* [22] administered 1 g L-carnitine i.v. after each dialysis session and this reduced rhEpo requirement from 102 ± 52.6 to 63.3 ± 37.8 U/kg/week, while the rhEpo requirement remained constant in the placebo group. In 14 haemodialysis patients under maintenance rhEpo therapy 0.04–0.06 g/kg/week L-carnitine i.v. (corresponding to 1 g L-carnitine at the end of each dialysis) resulted in a decrease in rhEpo requirement from 151 ± 30.6 to 87.5 ± 31.6 U/kg/week. Haemoglobin levels were unchanged or even increased in L-carnitine-treated patients despite a significantly reduced rhEpo dose. In a recent placebo-controlled study, Kletzmayr *et al.* [4] reported a reduced rhEpo requirement ($-36.9 \pm 23\%$) in 42% of 20 haemodialysis patients treated with carnitine (5 or 25 mg/kg/dialysis i.v. after each dialysis session). Fifty-eight per cent of patients did not respond to the L-carnitine therapy and maintenance of a stable haemoglobin necessitated a constant rhEpo dose. The authors did not find significant differences in free or total carnitine plasma concentrations between responders and non-responders. Carnitine concentrations tended to be higher in patients in whom anaemia improved under carnitine therapy. No significant correlation between plasma concentrations of free or total carnitine and rhEpo requirement or haemoglobin could be found. In 42 ESRD patients without carnitine treatment, Kooistra *et al.* [24] noted a significant correlation between rhEpo dose and total plasma carnitine concentration (Pearson correlation coefficient, 0.58; $P < 0.05$).

The mechanisms by which carnitine may have reduced the rhEpo requirement are still unknown. Kletzmayr *et al.* [4] did not see a significant increase in erythrocyte survival time in carnitine-treated patients. In contrast to previous clinical and experimental studies in non-Epo treated patients, there was no change in global osmotic fragility after carnitine therapy in rhEpo-treated patients [22]. Since Trovato *et al.* [14] reported a persistent increase of absolute reticulocyte count under carnitine therapy, mechanisms other than the improved stability of erythrocyte membranes must be considered to explain the Epo-saving effect of carnitine therapy in some, but not all, dialysis patients.

Therefore, the consensus group concluded that routine administration of carnitine cannot be recommended in dialysis patients today. This treatment should be reserved for patients with unexplained low response to Epo therapy [28].

In conclusion, when elevation of PTH, elevation of CRP and presence of aluminium intoxication has been excluded, carnitine therapy can be considered. In general plasma levels of free carnitine seem to be decreased despite an increase plasma levels of total carnitine. L-carnitine therapy may improve anaemia and reduce rhEpo requirements at least in a subgroup of haemodialysis patients. The optimal dose of carnitine therapy and also the pathophysiology of this improvement of renal anaemia under L-carnitine therapy are not clarified.

Acknowledgements. I thank Prof. Dr. Dr. mult.h.c. E. Ritz for suggestions and critical review.

References

1. Hörl WH. Is there a role for adjuvant therapy in patients being treated with epoetin? *Nephrol Dial Transplant* 1999; 14: 50–60
2. Rodriguez-Segade S, Alonso De la Pena C, Paz M *et al.* Carnitine concentrations in dialyzed and undialyzed patients with chronic renal insufficiency. *Ann Clin Biochem* 1986; 23: 671–675
3. Wanner C, Hörl WH. Carnitine abnormalities in patients with renal insufficiency: pathophysiological and therapeutic aspects. *Nephron* 1988; 50: 89–102
4. Kletzmayr J, Mayer G, Legenstein E *et al.* Anemia and carnitine supplementation in hemodialyzed patients. *Kidney Int* 1999; 69: S93–S106
5. Leschke M, Rumpf KW, Eisenhauer T *et al.* Quantitative assessment of carnitine loss during hemodialysis and hemofiltration. *Kidney Int* 1983; 24: S143–S146
6. Golper TA, Wolfson M, Achmad S *et al.* Multicenter trial of L-carnitine in maintenance hemodialysis patients I. Carnitine concentrations and lipid effects. *Kidney Int* 1990; 38: 904–911
7. Mingardi G, Bizzi A, Cini M, Licini R, Mecca G, Garatini S. Carnitine balance in hemodialyzed patients. *Clin Nephrol* 1980; 13: 269–270
8. Bàhmer T, Rydning A, Solberg HE. Carnitine levels in human serum in health and disease. *Clin Chim Acta* 1974; 57: 55–61
9. Matsumura M, Hatekeyama S, Koni I, Mabuchi H, Muraboto H. Correlation between serum carnitine levels and erythrocyte osmotic fragility in hemodialysis patients. *Nephron* 1996; 72: 574–578
10. Bellinghieri G, Savica V, Mallamace A *et al.* Correlation between increased serum and tissue L-carnitine levels and improved muscle symptoms in hemodialyzed patients. *Am J Clin Nutr* 1983; 38: 523–531
11. Savica V, Bellinghieri G, Di Stefano C *et al.* Plasma and muscle carnitine levels in hemodialysis patients with morphological—ultrastructural examination of muscle samples. *Nephron* 1983; 35: 232–236
12. Wanner CH, Wäckerle B, Boeckle H, Schollmeyer P, Hörl WH. Plasma and red blood cell carnitine and carnitine esters during L-carnitine therapy in hemodialysis patients. *Am J Clin Nutr* 1990; 51: 407–410
13. Jackson JM, Lee HA. L-carnitine and acetyl-L-carnitine status during hemodialysis with acetate in humans: a kinetic analysis. *Am J Clin Nutr* 1996; 64: 922–927
14. Trovato GM, Ginardi V, DiMarco V, Dell'Aira A, Corsi M. Long-term L-carnitine treatment of chronic anemia of patients with end-stage renal failure. *Curr Ther. Res* 1982; 31: 1042–1049
15. Shaw AG. Hemolysis in chronic renal failure. *Br Med J* 1967; 11: 213–244
16. Bayon JE, Alvarez AI, Barrio JP, Diez C, Prieto JG. Effects of stanozolol and L-carnitine on erythrocyte osmotic fragility during aerobic exercise in rats. *Comp Haematol Int* 1993; 3: 196–200
17. Arduini A, Rossi M, Mancinelli G *et al.* Effect of L-carnitine and acetyl-L-carnitine on the human erythrocyte membrane stability and deformability. *Life Sci* 1990; 47: 2395–2400
18. Farrell S, Vogel J, Bieber LL. Entry of acetyl-C-carnitine into biosynthetic pathways. *Biochim Biophys Acta* 1986; 876: 175–177
19. Donatelli A, Terrizzi C, Zummo G, Russo V, Bucalo ML, Scarpinato A. Effects of L-carnitine on chronic anemia and erythrocyte adenosine triphosphate concentration in hemodialysis patients. *Curr Ther Res* 1987; 41: 620–624
20. Izumo H, Izumo S, DeLuise M, Flier JS. Erythrocyte Na,K pump in uremia. Acute correction of a transport defect by hemodialysis. *J Clin Invest* 1984; 74: 581–588
21. Cheng JT, Kahn T, Kaji DM. Mechanism of alteration of sodium potassium pump of erythrocytes from patients with chronic renal failure. *J Clin Invest* 1984; 74: 1811–1820
22. Labonia WD, Morelli JR, Gimenez MI, Freuler PV, Morelli OH. Effect of L-carnitine on sodium transport in erythrocytes from dialyzed uremic patients. *Kidney Int* 1987; 32: 754–759
23. Albertazzi A, Capelli P, Di Paolo B, Pola P, Tondi P, Vaccario O. Endocrine metabolic effects of L-carnitine in patients on regular dialysis treatment. *Proc EDTA* 1982; 19: 302–307
24. Kooistra MP, Struyvenberg A, Van Es A. The response of recombinant human erythropoietin in patients with the anemia of end-stage renal disease is correlated with serum carnitine levels. *Nephron* 1991; 57: 127–128
25. Boran M, Calva I, Görenc F, Cetin S. Response to recombinant human erythropoietin (r-Hu EPO) and L-carnitine combination in patients with anemia of end-stage renal disease. *Nephron* 1996; 73: 314–315
26. Patrikarea A, Stamelou K, Ntaontaki I, Patadakis IT. The effect of combined L-carnitine and erythropoietin administration on the anemia and on the lipid profile of patients on hemodialysis. EDTA Annual Congress, Amsterdam, 18–21 June 1996, Abstracts. *Nephrol Dial Transplant* 1996; 11: A262
27. Karvadias D, Fortounas C, Tsouchnikas J, Vlachononasios T, Barboutis K. Reduction of the cost of erythropoietin therapy by coadministration of L-carnitine in hemodialysis patients. EDTA 32nd Congress, 1995, Athens, Greece
28. Consensus Group Statement. Role of L-carnitine in treating renal dialysis patients. *Dial Transplant* 1994; 23: 177–181