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Original article

L-carnitine supplementation in patients with cystic acne on isotretinoin therapy ☆

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Abstract

Background Patients with cystic acne (CA) on Isotretinoin (Iso) therapy might present muscular symptoms as side effect of the drug. Myalgia, weakness, hypotension are also some of the main characteristics of carnitine (car) deficiency.

Methods Two hundred and thirty ($N = 230$) patients with CA were treated with Isotretinoin (0.5 mg/kg per 24 h). All the patients were requested to visit our out-patient department at the onset of muscular symptoms. Laboratory tests including car (total, free, acylcarnitine) were determined in blood and urine before treatment, at the onset of muscular symptoms and after the end of a 45 day study. Fifty percent of the patients with muscular involvement received L-carnitine (100 mg/kg per 24 h per os) (group C) and 50% placebo (group P).

Results Their laboratory tests showed the well known increases of their liver enzymes and lipids, whereas car blood levels were remarkably decreased at the onset of their muscular symptoms and or at the end of the study. Their supplementation with L-car, in patients of group C ($N = 20$) without Iso discontinuation or reduction, resulted in the disappearance of their muscular symptoms within 5–6 days and normalisation not only of the increased levels of their liver enzymes but also those of car, at the 45 day of their therapy. Additionally, the patients who received placebo (group P, $N = 20$) continued complaining for mualgias. The rest of the patients (group A, $N = 190$) did not experience any muscular symptoms, their laboratory tests showed elevation of liver enzymes and lipids and a decrease in car levels in the blood whereas a remarkable increase of car excretion was determined in their urine.

Conclusions Iso therapy decreases car blood levels in patients with CA. L-car supplementation might treat liver and muscular side effects of the drug. These hopeful preliminary results need further investigation.

Keywords: Cystic acue; Isotretinoin; L-carnitine

1. Introduction

L-carnitine (β-hydroxy-γ-trimethylaminobuturica-cid) is a small water soluble molecule important in mammalian metabolism. It is essential for the normal oxidation of fats by the mitochondria and is involved in the transesterification and excretion of acyl - CoA esters, the oxidation of branched chain α-ketoacids, and removal of potential toxic acylcarnitine esters from within mitochondria. Quantitative reductions in total and/or acylcarnitine concentrations and changes in the concentration of different acylcarnitine species are known to occur in a number of inherited or acquired disorders [1–3].

Furthermore, there are a number of reports of acquired carnitine (car) deficiency in patients on treatment with Sodium Valproate some of which detail

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disturbances in mitochondrial β-oxidation [4–6]. On the other hand, musculoskeletal pain or mild discomfort are observed when systemic retinoids are administered. The upper trunk, middle and lower part of the thoracic and lumbar spine, and the muscles of the legs are usually involved. Occasionally it may be necessary in reduce or discontinue the treatment with Isotretinoin (Iso) [7,8].

Since inherited or acquired car deficiency has been reported to induce myalgia or muscle discomfort which are also characteristic side effects of Iso, it is speculated that these findings of a possible acquired car deficiency in Iso treated patients should be investigated, The aim of this study was to estimate car levels in blood and urine in patients with cystic acne (CA) before and after 45 days on treatment with Iso and to evaluate whether or not the supplementation with L-carnitine could treat the muscular symptoms presented as side effects of the drug.

2. Patients and methods

2.1. Patients

A high sample of two hundred and thirty ($N = 230$) patients with CA (121 F, 109 M) mean age 20.8 $\pm$ 1.5 years were treated with Iso (Ro – Accutane 0.5 mg/kg per 24 h). Fifty ($N = 50$) medical students of comparable age and sex were the control group.

The patients were requested to visit our out-patient department at the onset of any muscular problem for clinical and laboratory evaluation. Fifty percent of the patients with muscular involvement should receive L-car (100 mg/kg per 24 h) (group C) and 50% placebo (group P).

In patients as well as in controls there was no history of excessive physical activity, intercurrent illness including infection, additional drug (i.e. contraceptives, antiepilephic etr) or alcohol intake, or passing of dark red urine.

2.2. Methods

Six millilitres of blood was drawn for the estimation of liver function (SGOT, SGPT. alk. phosphatase, total protein, γGt), lipid evaluation (cholesterol, triglycerides, HDL, LDL, VLDL) as well as for creatine kinase and aldolase. Tests for antibodies against skeletal and smooth muscles, LE cells, complement, antinuclear antibodies, rheumatoid factor and protein electrophoresis were also evaluated.

Plasma and urine carnitine concentrations were determined by a radioenzymatic assay. Free car values were measured before and total car measured after alkaline hydrolysis, The levels of acylcarnitine were evaluated by determining the difference between total car and total acid soluble car [9].

All the above tests were performed in the patients before the initiation and after a 45 day period on treatment, and in controls only once. The same laboratory investigations were re-evaluated in those of patients, who complained of myalgia, at the onset of their symptoms. Estimation of total car contents in muscles was not permitted by our ethical committee.

2.2.1. Statistical analysis

t-Paired test as well as *t*-tests for repeated measures were utilised for the statistical analysis of the results. $P < 0.05$ was considered statistically significant.

3. Results

Mild myalgia and moderate stiffness of their lower extremities were clinically observed in 40/230 (16%) patients after 11–19 days (mean 15 $\pm$ 4 days) on treatment with Iso. On examination muscle tenderness of their affected muscles was present without weakness or wasting. These symptoms disappeared in the patients of group C ($N = 20$) on L-carnitine treatment, after 5–6 days, without reduction or discontinuation of Iso therapy.

On the contrary, the patients on placebo (group P, $N = 20$) continued complaining for such symptoms, two discontinued their treatment, four received systemic analgesic therapy and the rest of them experienced mild myalgias.

On the other hand, as shown in Tables 1, 2 and 3, there was a statistically significant elevation of their muscular and liver enzymes as well as a reduction of blood car levels in patients of groups A and P at the end of this study. Additionally, the same laboratory results were observed in the patients of groups C and P (Tables 2 and 3) at the onset of their symptoms whereas non statistical differences in the results of these tests were observed in group C at the end of a

Table 1
Laboratory tests in patients of group A ($N = 190$) before and after 45 days treatment vs. controls[a]

Tests	Before	After	Controls
SGOT (units/l)	27 ± 7*	39 ± 9.0*	26.5 ± 7.5
SGPT (units/l)	21 ± 8*	37.0 ± 9.5*	2.3 ± 9.5
Al.Ph (units/l)	74 ± 24*	86.0 ± 28*	76 ± 24
γGt (units/l)	12 ± 3*	17.8 ± 7.0*	13 ± 4
CPK (units/l)	96 ± 5.5**	128 ± 9.8**	93 ± 5.0
Ald (units/l)	104 ± 12**	126 ± 14**	110 ± 14
Total protein (g/l)	7.6 ± 0.4	7.7 ± 0.5	7.5 ± 0.5
Chol (mM/l)	54.3 ± 9*	60.7 ± 10*	52 ± 10
Trig (mM/l)	0.63 ± 0.3**	0.92 ± 0.6**	0.61 ± 0.3
HDL (mM/l)	2.57 ± 1.2**	2.0 ± 1.3**	2.53 ± 1.3
LDL (mM/l)	1.53 ± 1.3**	1.89 ± 1.4**	1.55 ± 1.4
VLDL (mM/l)	0.52 ± 0.1*	0.71 ± 10*	0.54 ± 0.2
Blood (μmol/l)			
T.car	18.0 ± 4.4*	12.7 ± 2.5*	17.9 ± 5.8
F.car	14.0 ± 3.0*	9.9 ± 2.4*	15.0 ± 4.3
AC	3.7 ± 2.5**	4.76 ± 1.3**	3.1 ± 1.2
AC/F	0.21 ± 0.03*	0.51 ± 0.05*	0.22 ± 0.01
Urine (μmol/l)			
T.car	16 ± 14**	25 ± 10**	15 ± 10
Free	10 ± 5	14 ± 6	9 ± 5

[a] Values are expressed as mean ± SD; $*P < 0.01$, $**P < 0.05$.

45 day therapy with Iso plus car (Table 3). Total protein, showed no significant differences in all groups of patients.

Furthermore, Chol, LDL, VLDL and triclycerides were elevated, HDL was reduced in the groups of patients.

4. Discussion

Treatment with Iso has been reported to increase the concentrations of serum cholesterol, triglycerides, LDL and VLDL and to reduce HDL as were found in all the groups of patients [8,10,11]. Additionally, the liver and muscular enzymes were also elevated in the groups A and P at the end of this study and in the groups C and P before the establishment of L-car vs. placebo treatment, supplementation, these findings were also reported in previous studies [8,10,11].

Furthermore, in group A (Table 1) at the 45 day of therapy and in patients of groups C and P (Tables 2 and 3) at the onset of their symptoms, car levels, total free, acylcarnitine were significantly decreased whereas the ratio AC/F and the excretion of car in urine were remarkably elevated. This could be due to some extend, to their liver dysfunction caused by Iso. Liver is the organ where car is synthesised from methionine and protein bound lysine [1,2]. Additionally significant loss of car occurs during haemodialysis and car deficiency has been suggested as a cause, or at least a contributory factor in the muscle weakness associated with chronic haemodialysis [12,13]. These symptoms, in a lesser degree were also observed in the patients of groups C and P. The absence of car deficiency symptoms in the majority of patients of group A could be due to either large amounts of car taken with the food or to a large stock of car in their muscle and or their lack of exercise [1,2]. Interestingly, there are a number of reports of car deficiency in patients on treatment with Sodium Valproate [5,6,14], some of which detailed disturbances in mitochondria oxidation [14]. Moreover, patients on Valproate developed cardiomyopathy, and other car deficiency symptoms i.e. myalgia, weakness etc. which were improved after L-car supplementation [5,6,14].

Also, the treatment with L-car has been recommended to prevent the fatal hepatotoxic effects associated with Valproic acid [14–17], Thioacetamide [18], and in patients after haemodialysis resulting in a reduction of their muscle cramps, hypotention and improvement in their exercise capacity [12,13]. These results were in agreement with our findings in the patients of group C (Table 3) whose symptoms not only were ameliorated within 5–6 days on L-car treatment, but also the elevated levels of their liver and muscular enzymes declined to normal, It is suggested that L-car may induce protection or recovery from the 'injury' caused by Iso. Moreover, Walter [1] showed that although L-car supplementation could bring plasma car concentrations within normal range, muscle levels remained less than 5% of control values despite treatment, but this appeared to be sufficient for normal fat oxidation within muscle [1]. On the contrary, the presence of muscular symptoms in patients of group P (on placebo) could be due either to a minor subclinical disorder of fat metabolism related to car insufficiency, or to the absence of car in their food (vegetarians) [19] and or to a low stock of car in their muscle.

Although, there are good theoretical reasons for using L-car supplementation in patients on Iso therapy

Table 2
Laboratory tests in patients of group P ($N = 20$) before Iso treatment, at the onset of muscular symptoms and after 45 days treatment vs. controls[a]

Tests	Before	Onset of symptoms	After	Controls
SGOT (units/l)	25.6 ± 8.0	37.5 ± 8.0*	39.6 ± 9.2*	26.5 ± 7.5
SGPT (units/l)	22.6 ± 9.0	34.9 ± 9.5*	35.6 ± 10.0*	2.3 ± 9.5
Al.Ph (units/l)	76.0 ± 25.0	78.0 ± 20**	80.0 ± 18.0**	76 ± 24
γGt (units/l)	12.0 ± 5.2	22.0 ± 9.0*	24.0 ± 8.1*	13 ± 4
CPK (units/l)	98.5 ± 6.5	108 ± 10**	112 ± 10.6**	93 ± 5.0
Ald (units/l)	112.0 ± 13.0	148 ± 18**	150 ± 15.0**	110 ± 14
Total protein (g/l)	7.5 ± 0.6	7.6 ± 0.7	7.8 ± 0.6	7.5 ± 0.5
Chol (mM/l)	55.0 ± 10.0	69.0 ± 10*	68.0 ± 9.0*	52 ± 10
Trig (mM/l)	0.6 ± 0.1	0.95 ± 0.3*	0.92 ± 0.5*	0.61 ± 0.3
HDL (mM/l)	2.9 ± 1.4	2.5 ± 1.5**	2.3 ± 1.5**	2.53 ± 1.3
LDL (mM/l)	1.6 ± 1.4**	1.99 ± 1.5**	1.9 ± 2.0**	1.55 ± 1.4
VLDL (mM/l)	0.5 ± 0.2*	0.91 ± 0.2*	0.84 ± 0.3*	0.54 ± 0.2
Blood (μmol/l)				
T.car	16.4 ± 5.8	11.9 ± 2.5*	13.0 ± 1.2**	17.9 ± 5.8
F.car	12.3 ± 4.6	8.9 ± 2.5*	10.7 ± 4.5**	15.0 ± 4.3
AC	3.05 ± 1.2	3.9 ± 1.3*	4.19 ± 1.2**	3.1 ± 1.2
AC/F	0.24 ± 0.02	0.4 ± 0.04*	0.45 ± 0.01*	0.22 ± 0.01
Urine (μmol/l)				
T.car	15.0 ± 6.0	30 ± 12*	28 ± 10*	15 ± 10
Free	9.0 ± 4.0	12 ± 9**	13 ± 9*	9 ± 5

[a] Values are expressed as mean ± SD; *$P < 0.01$, **$P < 0.05$.

Table 3
Laboratory tests in patients of group C ($N = 20$) before Isotretion treatment, at the onset of muscular symptoms and at the end of the study[a]

Tests	Before	Onset of symptoms	After	Controls
SGOT (units/l)	24 ± 8.2*	39 ± 10*	21 ± 10.2	26.5 ± 7.5
SGPT (units/l)	20 ± 8.6*	39 ± 10*	25 ± 6.5	2.3 ± 9.5
Al.Ph (units/l)	75 ± 25*	88 ± 29*	78 ± 2.1	76 ± 24
γGt (units/l)	12 ± 5.1*	18.0 ± 8*	15 ± 7.6	13 ± 4
CPK (units/l)	97 ± 6.0**	135 ± 10**	103 ± 9.0	93 ± 5.0
Ald (units/l)	110 ± 13**	135 ± 14**	112 ± 15	110 ± 14
Total protein (g/l)	7.4 ± 0.5	7.7 ± 0.5	7.6 ± 0.8	7.5 ± 0.5
Chol (mM/l)	56 ± 10*	66.5 ± 11*	60 ± 10	52 ± 10
Trig (mM/l)	0.68 ± 0.5*	0.98 ± 0.8*	0.70 ± 0.7	0.61 ± 0.3
HDL (mM/l)	2.78 ± 1.4**	2.31 ± 1.4**	2.5 ± 1.5	2.53 ± 1.3
LDL (mM/l)	1.62 ± 1.4**	1.99 ± 1.5**	1.6 ± 1.5	1.55 ± 1.4
VLDL (mM/l)	0.50 ± 0.3*	0.75 ± 0.3*	0.60 ± 0.5	0.54 ± 0.2
Blood (μmol/l)				
T.car	19.0 ± 5.0*	11.9 ± 2.5*	16.2 ± 6.8	17.9 ± 5.8
F.car	15.0 ± 3.9*	8.9 ± 2.5*	13.0 ± 4.5	15.0 ± 4.3
AC	3.9 ± 2.5*	6.9 ± 1.4*	5.4 ± 1.6	3.1 ± 1.2
AC/F	0.22 ± 0.03*	0.42 ± 0.04*	0.25 ± 0.04	0.22 ± 0.01
Urine (μmol/l)				
T.car	17 ± 8*	30 ± 12*	19 ± 10	15 ± 10
Free	11 ± 5**	15 ± 9**	12 ± 8	9 ± 5

[a] Values are expressed as mean ± SD; *$P < 0.01$, **$P < 0.5$.

with muscular symptoms. placebo controlled trials in a greater number of patients are necessary to confirm these hopeful preliminary results.

References

[1] Walter I. Carnitine. Arch Dis child 1996;14:475–478.
[2] Bieber LL. Carnitine. Ann Rev Biochem 1988;57:261–283.
[3] Rebuche CI. Carnitine function and requirements during the life cycle. FASEB I 1992;6:3379–3386.
[4] Thurston I, Stautiart R. Amelioration of adverse effects of valproic acid on ketogenesis and liver coenzyme A metabolism by co-treatment with pantothenate and carnitine in the developing mice. Possible clinical significance. Pediatr Res 1992;31:419–423.
[5] Opala G, Winter S, Vance C. The effect of Valproic acid on plasma carnitine levels. Am I Dis Child 1991;145:999–1001.
[6] Melegh B. Kerner. I., Ascadia, G. L-carnitine replacement therapy on chronic Valproic treatment. Neuropediatr 1990;21:40–43.
[7] Mills C, Marks R. Adverse reactions to oral retinoids. Drug Safety 1993;9:280–290.
[8] Katz RA, Mergensen H, Nigra T. Elevation of serum triglyceride levels from oral Isotretinoin. Arch Dermatol 1980;116:1369–1372.
[9] McGarry ID, Foster DW. An improved and simplified radioisotopic assay for the determination of free and esterified carnitine. J Lipid Res 1976;17:277–281.
[10] Georgala S, Schulpis K, Potouridou I. Effects of Isotretinoin therapy on lipoprotein (a) serum levels. Int J Dermatol 1997;36:863–864.
[11] Marsen IR. Lipid metabolism and retinoid therapy. Pharm Ther 1989;40:55–65.
[12] Fagher B, Cederblad G, Eriksson M. L-carnitine and haemodyalisis double blind study on muscle function and metabolism. Scand I Clin Lab Invest 1985;45:169–178.
[13] Rogerson ME, Rylane PB, Wilson R. Carnitine and weakness in heamodialysis patients. Nephron Dial Transplant 1989;4:366–371.
[14] Melegh B, Pap M, Morava E. Carnitine dependent changes of metabolic fuel consumption during long term treatment with Valproic. J Pediatr 1994;25:317–321.
[15] Stantley CA, Delleu S, Coates PM. Chronic cardiomyopathy and weakness in children with a defect in carnitine uptake. Pediatr Res 1996;120:76–80.
[16] Erikson BO, Gustafsen B, Nordin I. Transport of carnitine into cells in hereditary carnitinedeficiency. J Inher Metab Dis 1989;12:108–111.
[17] Mantel H, Africk D, Blutter M. The importance of recognising secondary carnitine deficiency in organic acidaenias J Inher Metab Dis 1988;11:397–402.
[18] Chanda S, Mehendale H. Role of nutritional fatty acid and L-carnitine in the final outcome of thioacetamide hepatotoxicity. FASEB I 1994;8:1061–1068.
[19] Schulpis KH, Nounopoylos C, Tsagarakis S. Serum carnitine levels in phenylketonouric children under dietary control. Acta Pediatrica 1990;79:930–934.