ANTIARRHYTHMIC THERAPY WITH L-CARNITINE IN ACUTE MYOCARDIAL INFARCTION

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Summary

Carnitine, a substance similar to the amino acids, plays an important physiological role in fatty acid transport and metabolism and in energy production of the myocardial cell. L-carnitine in high dose has been postulated to have an antiarrhythmic effect and this has also been clinically proven. We studied 20 patients with actue myocardial infarction (AMI), 4 - 12 hours after the onset of their pain. The patients were randomized and treated double-blind with 5 g L-carnitine (N = 12) or placebo (N = 8) at hours 0, 12, 24, 36 and with 2 x 3 g on days 3 to 7 by intravenous infusion over 2 hours. The groups were similar for age (47 - 74 years), sex (15 m, 5 f), infarct site (9 anterior, 5 inferior, 6 mixed), maximum CPK and conventional antiarrhythmic therapy. 24-hour Holter-ECG was performed on days 1, 2, and 7 and showed no significant difference between the two groups for the incidence of ventricular extrasystoles (VES) per hour. On the second day following the AMI, however, only 4 of 12 carnitine-treated patients showed high-grade VES (Lown IVa and IVb), in comparison with 7 of 8 patients in the placebo group. The difference is significant, P = 0.028 (Fisher's-Exact-Test). Carnitine was well tolerated and antiarrhythmic efficacy was demonstrated on the second day following AMI.

Introduction

Carnitine, a physiological substance similar to the amino acids (table 1), plays a key role in fatty acid metabolism and energy production in the muscle cell. More than 95 % of total body carnitine is stored in skeletal or myocardial muscle tissue. Carnitine is principally synthesized in the liver from the amino acids lysine and methionine. It is also absorbed by the oral route and principally eliminated by the kidney.

Long chain activated fatty acids (acyl CoA) are the energy substrates of muscle cells and the principle source of energy for the myocardium. However, they cannot pass into the inner mitochondrial matrix. By binding to carnitine, CoA is liberated and acyl-carnitine can then pass from the cytosol into the mitochondria where the fatty acids are oxidized and ATP produced.

Carnitine is free to leave the mitochondria and is then available for further fatty acid transport activities. In the presence of ischemia or defects of beta-oxidation, long chain fatty acids cannot be oxidized and therefore accumulate. Carnitine can remove these unwanted fatty acids from the mitochondria and from the cell (1, 2). Carnitine is excreted in the urine as acyl-carnitine, resulting in a secondary myocardial carnitine deficiency (3 - 7). Accumulated fatty acids are toxic. They act negatively on the citric acid cycle by inhibiting citric acid synthesis, and they also inhibit adenosine-nucleotide-translocase (8), which transports ATP from the mitochondria into the cytosol. This results in low ATP concentrations in the cytosol of the myocardial cell, and ventricular arrhythmias may occur more easily (9, 10). From a pathophysiological point of view, it would thus be useful to eliminate completely the long chain fatty acids that accumulate in ischemic states. This can be achieved by administering high doses of carnitine. In acute myocardial infarction, urinary acyl-carnitine excretion increases during carnitine therapy by more than ten-fold (1). In addition, the effect of carnitine is to produce more acetyl-CoA from pyruvate instead of producing lactate (11 - 13). Removal of accumulated fatty acids, leading to increase in cytosolic ATP-concentration and decreased lactate production can explain the positive effects of carnitine both in animal ischemia experiments and in the clinically observed myocardial protective effect.

In order to evaluate the antiarrhythmic effect of carnitine in acute myocardial infarction, we performed a double-blind randomized placebo-controlled study in 20 patients.

Materials and methods

20 patients with acute myocardial infarction were studied, having obtained their informed consent and the approval of the Ethical Committee. The entry criteria were: age under 75 years and onset of pain 4 - 12 hours before admission to the hospital. Previous thrombolytic therapy had not been performed. Exclusion criteria: previous antiarrhythmic treatment with lidocaine or amiodarone, complete AV-block, pacemaker-implantation or hypokalaemia less than 3,2 mmol/l (table 2).

On days 1 and 2 both patient groups received double-blind 5 g carnitine or placebo intravenously every 12 hours in an infusion over 2 hours. This was followed by 3 g intravenously on days 3 to 7. A 24-hour-Holter-ECG was performed on days 1, 2 and 7.

The Holter tracings for rhythm and ST-segment analysis were performed using a Hellige Memoport c-apparatus with 2 channel recorder. The statistical evaluation was carried out using Fisher's-Exact-Test for the frequency of VES and the difference between the Lown-classification groups. The Pearson-Chi-Square-test was also used in addition to Fishers's-Exact-Test in order to compare the two patient groups. A difference was regarded as significant at $p < 0.05$ (two tail).

Results

There were no significant differences between the carnitine-treated patient group (N = 12) and the control-group (N = 8) in relation to age, sex, infarct site, maximum CPK, lidocaine therapy in the acute phase or secondary prophylactic beta-blocker treatment from third day (table 2). The mean age was 59.4 ± 7.6 (46 - 71) years in the carnitine group and 65.6 ± 9,9 (47 -74) years in the control-group (not significant). The values for maximum CPK were 1'327 ± 690 (L-carnitine) and 1'160 ± 1'205 U/L (control-group, not significant, mean ± SD). Furthermore, in relation to conventional antiarrhythmic therapy, particularly with lidocaine following entry into the study in the acute phase, no significant difference in the small number of patients could be observed. All patients received analgesics, nitrates, sedatives and heparin. No patients received amiodarone or digoxin. The incidence of single VES per hour in all the Holter-ECG-analyses on days 1, 2 and 7 was similar in both groups (table 3). A significant difference could be demonstrated on day 2 after the AMI in the Lown-classification, using Fisher's-Exact-Test. This was because there were significantly less high-grade arrhythmias of Lown-classes IVa and IVb in the carnitine group compared with the control group ($p = 0.028$, table 4). The difference was particularly striking for short-lasting ventricular tachycardiae of 4 - 10 beats, which only occurred in the control-group (4 of 8 versus 0 of 12 in the carnitine-group, $p = 0.014$, table 5).

Longer-lasting ventricular tachycardiae were not observed in this small patient population, nor were life-threatening complications such as ventricular fibrillation, asystole or reinfarction. All 20 patients could be discharged in good general health on the seventh day. The relatively highly-dosed carnitine therapy was well tolerated. There were no reports of adverse events.

Discussion

In the small number of patients studied, we were able to observe an antiarrhythmic effect of carnitine on the second day following AMI. With carnitine-treatment there was a significantly lower incidence of high-grade arrhythmias of Lown-classes IVa and IVb.

A similar clinical antiarrhythmic effect with carnitine in AMI has recently been reported (1). Rizzon et al also found a decrease in the incidence of VES per hour in the carnitine group, in addition to a reduction in short-lasting ventricular tachycardiae, on the second day following AMI. The carnitine dose used was only slightly higher (100 mg/kg body weight). It is not clear if the incidence and severity of arrhythmias on the first and second day following AMI could be due to differing mechanisms of action. In both studies the significant carnitine effect was demonstrated on the second day after AMI. In experimental ischemia, intravenous carnitine has a myocardial protective effect within minutes (3, 11, 14), although the serum trough levels also increase on the second day during 12 hourly administration of carnitine (1). In our study, a Holter-ECG was also performed on the seventh day. This did not show ST-depression in any case and no significant antiarrhythmic effect of carnitine could be shown in our small patient population. In other recently published clinical studies, carnitine has shown a positive effect in peripheral arterial vascular disease by prolonging the walking distance (15), and in chronic stable angina pectoris by improving the onset, duration and degree of ST-depression induced by stress testing (11, 16, 17). Antiarrhythmic activity can now also be demonstrated in these first clinical controlled studies. It is interesting that a physiological endogenous substance, with excellent tolerability, can demonstrate these antiarrhythmic properties.

Although carnitine was discovered nearly 100 years ago and its significance in fatty acid metabolism has long been recognized, it is only recently that carnitine has found a wider clinical application (18).

More extensive larger clinical studies are necessary to confirm clinical efficacy and assess the role of carnitine in the routine therapy of ischemic heart disease and possibly also various forms of heart failure (19,20). Such large long-term follow-up studies could also find out if carnitine can positively influence prognosis after AMI by reducing life-threatening arrhythmias such as ventricular fibrillation in the actue and chronic phase, or decreasing the infarct size.

Literature

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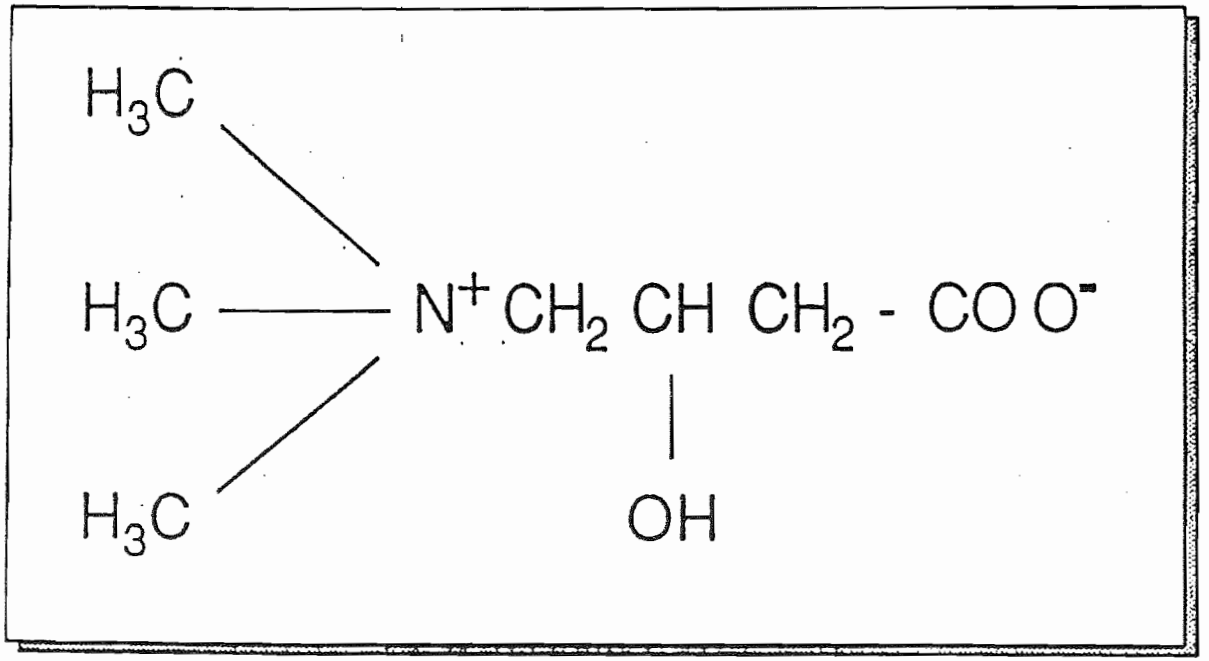
Table 1 Structure of L-Carnitine (3-hydroxy,-4-N-trimethylaminobutyric acid)


H3C
H3C
H3C
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OH