N.DOC.5913

DRUGS EXPTL. CLIN. RES. X(4) 219-223 (1984)

BENEFICIAL EFFECTS OF L-CARNITINE IN THE REDUCTION OF THE NECROTIC AREA IN ACUTE MYOCARDIAL INFARCTION

REBUZZI A.G.,[1] SCHIAVONI G.,[1] AMICO C.M.,[1] MONTENERO A.S.,[1] MEO F.,[2] MANZOLI U.[1]

1) Department of Cardiology, S. Cuore Catholic University, Largo Gemelli 8, Rome.
2) Department of Biochemistry, S. Cuore Catholic University, Rome, Italy.

Summary: *Many studies have demonstrated the importance of the necrotic area for the prognosis of mortality and complications in myocardial infarction. The present paper reports the effects of early administration of L-carnitine (40 mg/kg/die) on the reduction of the necrotic area, measured by MB CPK release. Reduced MB-CPK release with a significant reduction of maximum value of MB-CPK was observed in the patients treated. There were no significant differences between patients treated earlier and those treated later (before or after the fourth hour from the onset of symptoms). L-carnitine thus appears to be a useful drug in acute myocardial infarction, both for its antiarrhythmic action, already reported in the literature, and for its significant reduction of the necrotic area, probably due to improved utilization of myocardial energetic substrates.*

Introduction

Many reports describe the importance of the necrotic tissue area as a relevant factor for the prognosis of mortality and complications in acute myocardial infarction (1-4).

This justifies the interest that, for many years, researchers and cardiologists have taken in the quantitative evaluation of the infarcted area (5-10).

One of the most reliable methods closely correlated with the necrotic area seems to be the measurement of some serum enzymes, particularly MB-CPK, which is related to the extent of infarcted myocardium measured at autopsy (11, 12).

Since it has been demonstrated that myocardial infarction is a dynamic event (13, 14) and that therapy can modify its evolution (15, 16), many drugs have been tested for this purpose (17-20).

The aim of the present study was to evaluate the influence of L-carnitine treatment on the extent of the necrotic area in patients with acute myocardial infarction.

Animal studies with L-carnitine have investigated the effect of this drug in protecting the myocardium from stress or hypoxia (21, 22), while in man its action on pain threshold induced by atrial pacing (23) or by exercise stress test (24) have been evaluated.

0378-6501/84/0400219 + 5 $02.00/0

Materials and methods

Twenty-two patients hospitalized in the authors' Intensive Care Unit for acute myocardial infarction were studied. In all cases the time interval between the beginning of the pain and hospitalization did not exceed eight hours.

The diagnosis of transmural myocardial infarction was based on clinical data and ECG, and was futher confirmed by the determination of the following enzymes: CPK, LHD, transaminases.

Criteria for exclusion were:

a) Initial level of CPK values over the normal;
b) Evident signs of heart failure;
c) Second and third degree AV block;
d) Presence of other severe cardiac pathology;
e) Administration of drug by i.m. route.

The 22 patients were divided into two groups. The first (treated) consisted of 12 patients, 7 with anterior necrosis, 5 with inferior necrosis, treated with L-carnitine. The second group (controls) consisted of 10 patients. The treated patients were then subdivided into two sub-groups: A - Treatment started within four hours of the onset of symptoms; B - Treatment started after more than four hours.

All patients received treatment with polarizing solution (glucose 5% 500 ml + insulin 5 I.U., + KCL 30 mEq at an infusion rate of 20 drops/min) and isosorbide dinitrate (10 mg four times daily).

L-carnitine was administered (40 mg/kg/die) to the treated group for the first five days of hospitalization.

Samples of blood were taken from all the patients at the moment of hospitalization and every four hours up to 48-72 hours. The blood was immediately centrifuged for 10 min at 3000 rpm.

The serum was then drawn and stored at −20°C until the moment of assay. Samples with evident haemolysis were not analysed.

The MB-CPK isoenzyme was determined by the R.I.A. method using a Cardio Check RIA Kit (Nuclear Medical Systems Inc.) (normal value ≤ 12.5 ng/ml).

The sensitivity of this method is 0.5 ng/tube.

For each patient the following values were determined:

1) Total quantity of isoenzyme

$$MB\text{-}CPK_r = E(T) * kd \int_0^T E(t)dt(25).$$

2) The constant of disappearance (kd) of isoenzyme from the blood (2).
3) The total release period (timed from the first value ≥ 12.5 ng/ml until maximum value).
4) The rhythm of MB-CPK release (ng/ml/h) obtained by dividing the MB-CPK$_r$ for the total release period.

The results are expressed as mean ± s.e. and the differences were analysed by Student's t-test for unpaired data.

Results

Clinical data on both groups are shown in Table I. It is evident that there were no significant dif-

Table I *Clinical characteristics of treated patients and controls.*

		Treated pts (n = 12)	Controls (n = 10)
Sex	F	3	2
	M	9	8
Age		57 ± 5	53 ± 6
Localization of infarction	Ant.	7	6
	Inf.	5	3
	Intramur.	—	1
Arterial pressure	syst.	140 ± 7	135 ± 9
	diast.	87 ± 5	78 ± 6

ferences with regard to sex, age, location of necrosis and arterial pressure on arrival in the intensive care unit.

Figure 1 shows the mean value ± s.e. of MB-CPK_r and the maximum level of MB-CPK reached, the rate of release and its duration.

The figure shows that in treated subjects there was reduced MB-CPK release and, furthermore,

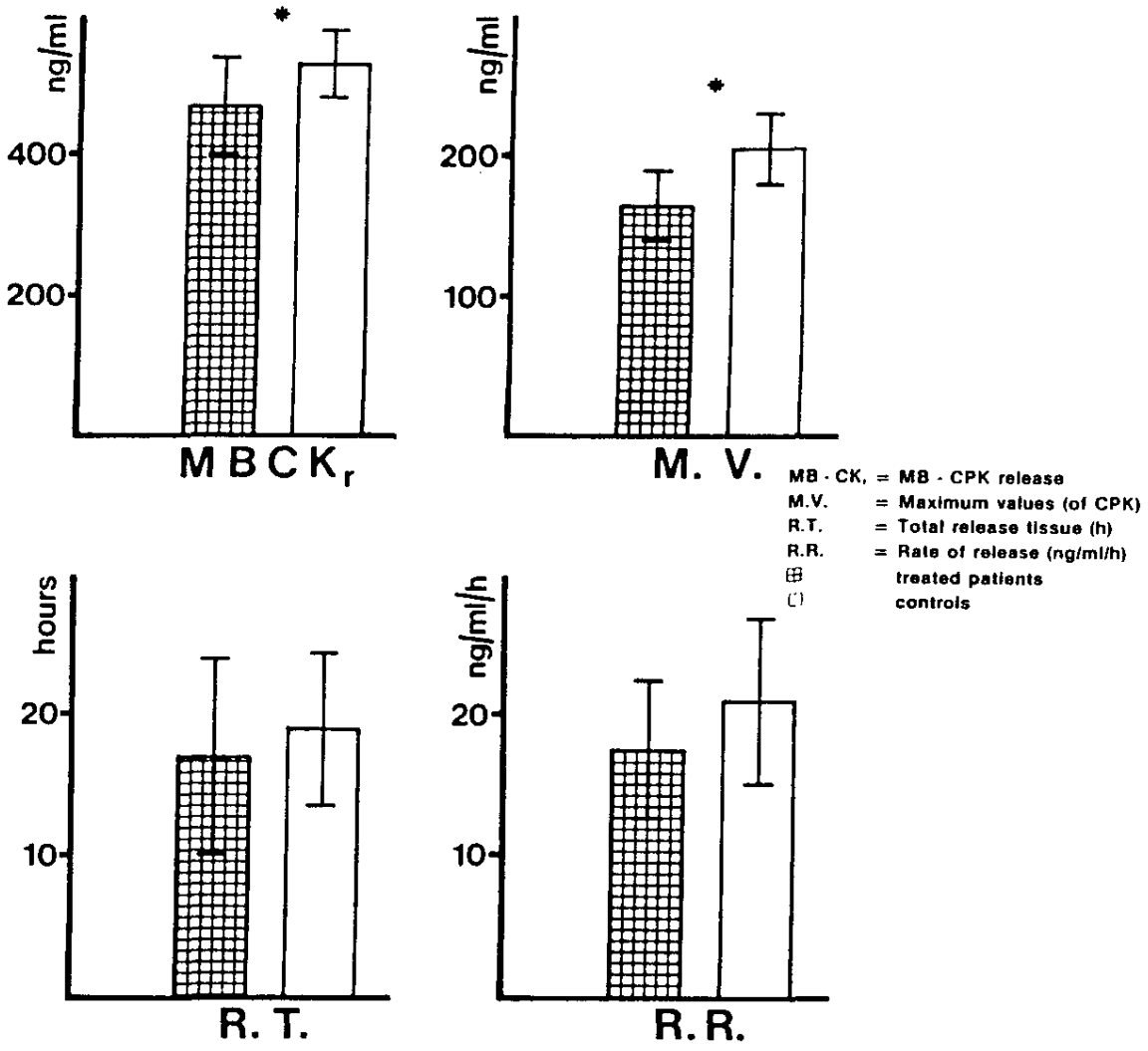

Fig. 1 Mean values ± s.e. of MB-CPK_r, maximum values of MB-CPK reached, rate and duration of release.

the maximum enzyme value was inferior to that found in the controls. The time and rate of enzyme release appeared to be reduced even if these values did not reach statistical significance.

There were no substantial differences between the two groups (0.00135 and 0.00127 min^{-1} respectively) with regard to the value of the constant of disappearance of isoenzyme.

During the observation period there were no evident clinical or radiological signs of cardiac failure in treated patients, while one patient in the control group underwent pulmonary oedema resolved by appropriate treatment (furosemide 40 mg × e.v. + digoxin 0.5 mg × e.v.).

There was no significant difference between the two sub-groups of treated patients but a tendency for improvement was observed in patients treated earlier.

One of the treated patients who arrived in the Intensive Care Unit with diagnosis of inferior-lateral infarction, exhibited second degree type I AV block on the second day, which receded after one more day.

None of the treated patients died during hospitalization in the Intensive Care Unit, while one patient from the control group died on the 35th day due to irreversible ventricular fibrillation.

Discussion

The present data seem to suggest that in acute myocardial infarction L-carnitine could have a beneficial effect in reducing the extent of the necrotic area. Moreover, in these patients there was a reduction in the maximum level of MB-CPK. In the treated patients a reduction was also observed in: 1) time of enzyme release; and 2) rhythm of release.

These data, although not statistically significant, permit us to hypothesize that L-carnitine is beneficial in the evolution of the ischaemic area of the myocardium.

There is no evidence of any significant differences in the parameters measured between patients given the drug within four hours of the onset of symptoms and those treated after four hours.

The literature reports significant differences in the effectiveness of beta-blockers (26-29) related to the time that treatment is started, while for verapamil such differences are less relevant (30).

It can be accepted that L-carnitine, even if not administered at once, functions as a "saving agent" for other ischaemic cells that are not yet affected in an irreversible way, probably by improving the utilization of energetic substrates in the myocardial cells (22, 31-33).

From the results of this research, admittedly carried out on a small group of patients, it can be considered that L-carnitine is a useful drug in acute phases of myocardial infarction for two reasons: first, because of the antiarrhythmic action already demonstrated (34); and secondly because of its significant effect on the reduction of the necrotic area, through improved utilization of energetic substrate in the myocardial cells.

Acknowledgements

We are deeply indebted to Sigma-Tau SpA (Rome) for suplying L-carnitine vials and to Miss Jacqueline Mallett for her technical assistance.

References

(1) Page D.L., Coulfield J.B., Kastor J.A., De Sanctis R.W., Sanders C.A. *Myocardial changes associated with cardiogenic shock.* New Engl. J. Med., **285**, 133, 1971.

(2) Norris K.M., Whitlock R.M.L., Barrat-Boyes C., Small C.W. *Clinical measurement of myocardial infarct size. Modification of a method for the estimation of total creatine phosphokinase release after myocardial infarction.* Circulation, **51**, 614, 1975.

(3) Sobel B.E., Bresnahan G.F., Shell W.E., Joder R.D. *Estimation of infarct size in man and its relation to prognosis.* Circulation, **46**, 460, 1972.

(4) Shell W.E., Sobel B.E. *Serum enzymes in myocardial infarction: diagnosis, prognosis and quantification.* In: Goodwin S.F., ed. "Progress in cardiology", Vol. IV. Lea & Febiger, Philadelphia, 1975.

(5) Bleifeld W.H., Hanrath P., Mathey D. *Serial CPK determinations for evaluation of size and development of acute myocardial infarction.* Circulation, **53** (Suppl. 1), 108, 1976.

(6) Mathey D., Bleifeld W., Buss H., Hanrath P. *Creatine kinase release in acute myocardial infarction: correlation with clinical, electrocardiographic and pathological findings.* Br. Heart. J., **76**, 1161, 1975.

(7) Roberts R., Henry P.D., Sobel B.E. *An improved basis for enzymatic estimation of infarct size.* Circulation, **52**, 743, 1975.

(8) Shell W.E., Kjekshus J.K., Sobel B.E. *Quantification assessment of the extent of myocardial infarction in the conscious dog by means of analysis of serial changes in serum creatine phosphokinase activity.* J. Clin. Invest., **50**, 2614, 1971.

(9) Shell W.E., Lavelle J.F., Covell J.W., Sabel B.E. *Early estimation of myocardial damage in conscious dogs and patients with evolving acute myocardial infarction.* J. Clin. Invest., **52**, 2579, 1973.

(10) Witteevens S.A.G.J., Hemker H.C., Hollaar L., Hermens W.T. *Quantitation of infarct size in man by means of plasma enzyme levels.* Br. Heart J., **37**, 795, 1975.

(11) Hillis L.D. *et al. Use of changes in the epicardial QRS complex to assess interventions which modify the extent of myocardial necrosis following coronary artery occlusion.* Circulation, **54**, 591, 1976.

(12) Norlander R., Kyquist O., Sylvén C. *Estimation of infarct size by creatine kinase.* Cardiology, **68**, 201, 1981.

(13) Alonso D.R., Scheitt S., Post M., Killij T. *Pathophysiology of cardiogenic shock. Quantification of myocardial necrosis, clinical pathologic and electrocardiographic correlations.* Circulation, **48**, 588, 1973.

(14) Chiche P. *Infarctus, nécrose et ischémie myocardiaque.* Coeur et Med. Int., **13**, 3, 1974.

(15) Maroko P.R., Braunwald E. *Effects of metabolic and pharmacologic intervention on myocardial infarct size following coronary occlusion.* Circulation, **53** (Suppl. I), 162, 1976.

(16) Maroko P.R. et al. *Factors influencing infarct size following experimental coronary artery occlusion.* Circulation, **43**, 67, 1971.

(17) Braunwald E., Maroko P.R. *The reduction of infarct size. An idea whose time (for testing) has come.* Circulation, **50**, 206, 1974.

(18) Jennings R.B., Reimer K.A. *Salvage of ischemic myocardium.* Mod. Conc. Cardiovasc. Dis., **43**, 125, 1974.

(19) Keith, Reimer K.A., Lowe J.W., Jennings R.B. *Myocardial ischemic cell death as a function of time.* Circulation, **54**, (Suppl. II), 67, 1976.

(20) Reimer K.A., Lowe J.W., Jennings R.B. *Effect of calcium antagonist verapamil on necrosis following temporary coronary artery occlusion in dogs.* Circulation, **55**, 581, 1977.

(21) Antico L. et al. Sui rapporti tra metabolismo e funzione cardiaca. Azione di alcune sub-strati-glucosio, aceto-acetato, aceto-acetil-carnitina sulla dinamica del cuore isolato. Chir. Pat. Sper., **XVI**, 27, 1968.

(22) Folts J.D., Shug A.L., Koke J.R., Bittar N. *Protection of the ischaemic dog myocardium with carnitine.* Am. J. Cardiol., **41**, 1209, 1978.

(23) Thomsen J.H., Yap V.U., Patel A.K. *Improved stress tolerance of the ischaemic human myocardium after carnitine administration.* Am. J. Cardiol., **300**, 43-2, 1979.

(24) Cherchi A., Fonzo F., Lai C., Mercuro G., Corsi M. *The influence of carnitine on stress tolerance in angina pectoris.* Boll. Soc. Ital. Cardiol., **XXIII**, 71, 1978.

(25) Roberts R., Henry P.D., Sobel B.E. *An improved basis for enzymatic estimation of infarct size.* Circulation, **52**, 743, 1975.

(26) Tavazei L., Salerno J.A., Ray M., Chimenti M., Ivaldi M. *Il propranololo nell'infarto acuto.* In: Proceedings of VIth ANMCO Congress, Pozzi, Rome, 1975, p. 259.

(27) Peter T., Norris R.M., Heng M.K., Singh B.M., Clarke E.D. *Reduction of creatinine kinase release after acute myocardial infarction by propranolol.* Circulation, **56** (Suppl. III), 240, 1977.

(28) Rassmussen M.M., Reimer K.A., Kloner R.A., Jennings R.B. *Infarct size reduction by propranolol before and after coronary ligation in dogs.* Circulation, **56**, 794, 1977.

(29) Reimer K.A., Lowe J.W., Rassmussen M.M., Jennings R.B. *The wave front phenomenon of ischemic cell death. I. Myocardial infarct size and duration of coronary occlusion in dogs.* Circulation, **56**, 786, 1977.

(30) Wolf R. et al. *Wirkung von Verapamil auf die Hämodynamik und Grosse des akuten Myokardinfarkts.* Herz, **2**, 110, 1977.

(31) Pande S.V. *A mitochondrial carnitine-acylcarnitine system.* Proc. Nat. Acad. Sci. USA, **72**, 883, 1975.

(32) Schwarz A. *Biochemical and morphologic correlates of cardiac ischemia.* Am. J. Cardiol., **32**, 46, 1973.

(33) Vick J.A., De Felice S.J., Sanzari U., Klein M. *Protective effects of carnitine in myocardial ischaemia.* The Physiologist, **19**, 111, 1976.

(34) Di Palma J.R., Ritchie D.M., McMichael R.F. *Cardiovascular and antiarrhythmic effects of carnitine.* Arch. Int. Pharmacodyn. Ther., **217**, 246, 1975.